Additional Chromosomal Abnormalities in Chronic Myeloid Leukemia Patient Treated with First-Line Tyrosine Kinase Inhibitor Therapy: Good or Poor Prognosis?

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ABSTRACT

A 33-year-old male came to Policlinic of Hematology-Medical Oncology Dr. Cipto Mangunkusumo General Hospital for routine control of chronic myeloid leukemia (CML) treatment. He was treated with Imatinib Mesylate (IM) for two years. At the beginning of therapy, he showed good treatment response. However, after two years of treatment, he lost complete hematological response (CHR) occured and major molecular response (MMR) was not achieved. This demonstrated drug resistance even with good compliance. Evaluation of therapy through cytogenetic karyotype testing showed complex additional chromosomal abnormalities (ACA) in addition to the Philadelphia chromosome (Ph). Tyrosine kinase inhibitor (TKI) therapy in this type of patients should be replaced with other alternative TKIs. A mutation profiling test is needed to determine alternative TKI. Monitoring in the treatment of CML patients is very important. The presence of ACA indicates disease progression and poor prognosis. Time to change therapy in CML patients must be done appropriately based on the results of hematological, molecular, and cytogenetic testing.

Keywords: *chronic myeloid leukemia (CML), additional chromosomal abnormalities, drug resistance*

INTRODUCTION

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder caused by translocation t(9;22)(q34;q11) that results in a Philadelphia chromosome (Ph).[1] When first diagnosed, most CML patients (90-95%) are in chronic phase.[1,2] The onset age of CML patients in Asia is lower than in western countries.[3] Proportion of Ph(+)/BCR-ABL(+) chronic phase (CP) CML patients in Dr. Cipto Mangunkusumo General Hospital is 90%.[4]

CML treatment has changed dramatically in the last decade. Imatinib and nilotinib are tyrosine kinase inhibitors (TKIs) which are commercially used for treatment of CML patients in Indonesia. Treatment with TKI results in 85-95% overall survival after five years.[5] Imatinib mesylate (IM) is the first TKI approved to treat CML-CP patients. IM competitively inhibits adenosine triphosphate (ATP) attachment sites on BCR-ABL oncoprotein, thus inhibiting phosphorylation of proteins involved in cell signal transduction. This efficiently inhibits BCR-ABL kinase, however, it also blocks platelet-derived growth factor (PDGF) receptors and KIT tyrosine kinase.[5]

We expected that CML patients who were treated with TKI to have prolonged survival which is similar to normal people. However, patients with CML responded differently to

TKI. We are reporting a case of a CML patient who showed disease progression after being treated with first-line IM therapy and showed additional chromosomal abnormalities (ACA) from cytogenetic testing.

CASE ILLUSTRATION

A 33-year-old male visited Polyclinic of Hematology-Medical Oncology Dr. Cipto Mangunkusumo General Hospital for his routine check-up of CML treatment. At the time of the visit, he had no complaints. He had been treated with oral IM 1 x 400 mg/day for two years. He had good compliance in taking his medication and did not take any other drugs. He had no history of any other diseases. He regularly came to Policlinic of Hematology-Medical Oncology for a check-up and to get IM. Physical examination did not show splenomegaly. After two years of IM therapy, laboratory testing revealed an increase in white blood cell (WBC) count to 91,140/uL (normal range: 4000-11,000/uL), platelet (Plt) count to 1,761,000/uL (normal range: 150,000-400,000/uL), basophil to 9% (normal range: 0-2%), myeloblast 1% (normal: no immature cells). Quantitative BCR-ABL was 63% IS. Bone marrow aspiration revealed a hypercellular morphology with M:E ratio 6.5:1 and expansion of granulopoiesis with 5.5% of blast cells.

On his first visit two years ago, he complained of feeling nauseous and bloated. Vital signs were normal. Physical examination indicated anemia in both eyes conjunctiva and massive splenomegaly (Schuffner 8). There was neither hepatomegaly nor any other abnormal findings. The result of blood test revealed anemia with hemoglobin (Hb) count of 5.9 g/dL (normal range: 13.2-17.3 g/dL), leukocytosis with WBC count of 251,030/uL, normal Plt value of 186,000/uL, basophil 1%, promyelocytes 1%, myeloblast 3%, and myelocytes 1%. He underwent bone marrow aspiration testing. Qualitative BCR-ABL testing was positive. Based on history, splenomegaly, peripheral blood, bone marrow aspiration, and BCR-ABL testing, we established the diagnosis of CML-CP. Sokal score was 1.3 points and Eutos score was 87 points.

DISCUSSION

Our patient was a 33-year old male who came to Policlinic of Hematology-Medical Oncology Dr. Cipto Mangunkusumo General Hospital with CML diagnosis who was treated with IM since two years ago. He routinely came for control of his IM treatment and had no complaints. We evaluated the treatment response of CML patients regularly. Response to TKI therapy is determined by the measurement of hematologic (normalization of peripheral blood counts), cytogenetic (decrease in the number of Ph-positive metaphases using bone marrow cytogenetics), and molecular responses (decrease in the amount of BCR-ABL chimeric mRNA using qPCR). The goal of TKI therapy is to achieve a complete hematologic response (CHR) within three months, a complete cytogenetic response (CCyR) and major molecular response (MMR) within 12 to 18 months after first-line TKI therapy and to prevent disease progression to accelerated or blastic phase or CML.[5,6] Since patients with CML on TKI are expected to live just like normal people, surrogate markers of outcome are important. Achieving a deeper response faster is associated with better outcome.[7]

This patient achieved CHR within three months after he started taking IM and continued the treatment until two years with good compliance. After two years of treatment, his peripheral blood counts revealed leukocytosis, thrombocytosis, basophilia, and the presence of immature cells. Quantitative BCR-ABL was 63% IS. Thus, the patient loss of CHR and did not achieve MMR after 24 months of imatinib therapy while he had no symptoms. We should evaluate patient compliance and drug interaction. In this patient, he had good compliance and did not take any other medications. Patients with disease that is resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting.[6]

We performed bone marrow aspiration and, despite the two-year treatment with IM, the bone marrow still showed hypercellular morphology and expansion of granulopoiesis with 5.5% of blast cells (**Figure 1**). Cytogenetic analysis showed complex additional chromosomal abnormalities (ACA) such as 41,Y,-X,-11,-16,-

17,-18[1]/44,XY,-17,-20[2]/45,XY,18[1]/45, XY,ob(13;22)(q10;q10),22[1]/46,XY,t(9;22) (934;q11)[2]/46,XY[6], while Ph was still there (**Figure 2**). Ideally, we also need to perform BCR-ABL mutation profiling to guide the selection of alternative TKI.[5-7] However, we have a limitation in performing mutation profiling due to lack of facilities.

Cytogenetic monitoring should be performed by analysis of marrow cell metaphases, reporting the proportion of Ph+ metaphases with 20 metaphases analyzed minimally. The cytogenetic response is defined as complete (CCyR) with 0% Ph+ metaphases, partial (PCyR) with 1%-35% Ph+ metaphases, minor with 36%-65% Ph+ metaphases, minimal with 66%-95% Ph+ metaphases, and none if >95% Ph+ metaphases.[5] Our patient did not achieve cytogenetic response at all at 2 years of treatment with IM, even the cytogenetic also showed additional chromosome abnormalities which indicate a warning to treatment response.

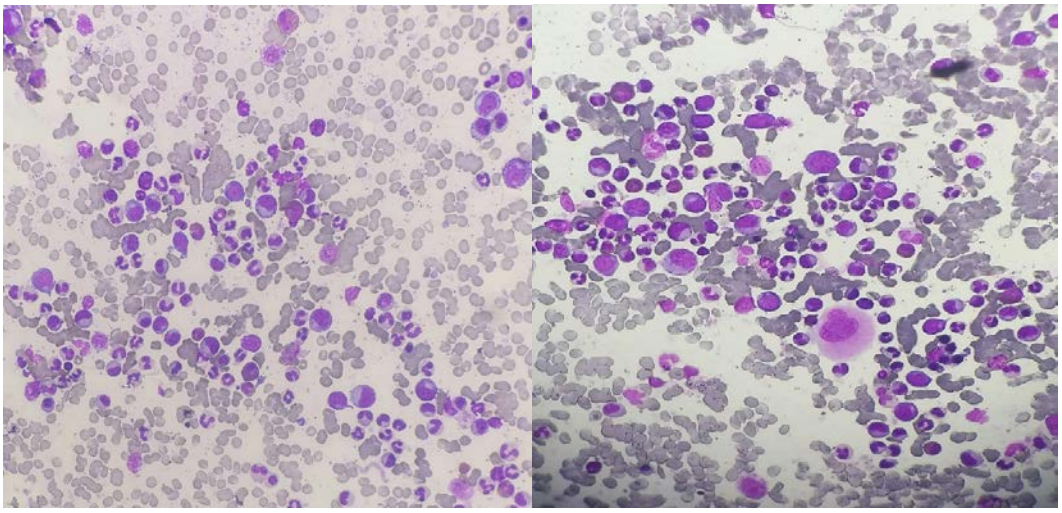

Figure 1. Morphology of bone marrow after 2 years on imatinib mesylate treatment.

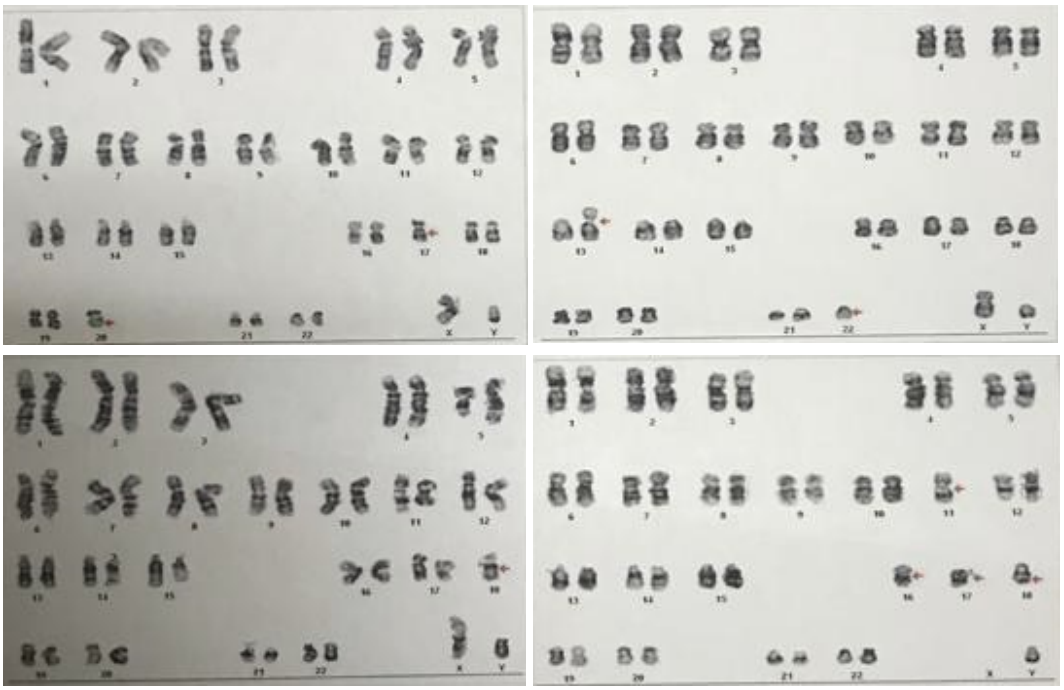

Figure 2. Cytogenetic testing after 2 years on imatinib treatment

The emergence of additional chromosomal abnormalities (ACAs) in Ph (+)/ BCR-ABL (+) CML, known as clonal evolution, is an indicator of multistep disease progression. It is a reflection of genetic instability that characterizes disease evolution in CML.[8,9] Beside for diagnosis, cytogenetics is an important tool for prognosis after treatment with TKI. Frequently, ACAs are found in Ph+ cells and interfere with the progression of CML. ACAs increase in the advanced stage, from 30% in accelerated phase to 80% in blastic crisis. ACAs are related to poor prognosis, with a lower rate of treatment response with Imatinib.[10,11] We believe that ACAs in our patient is a hallmark of poor prognosis to treatment with Imatinib, even ACAs also a sign of progression into an accelerated phase of CML so that we should change Imatinib to the second generation TKIs, such as nilotinib, dasatinib, or bosutinib, or even ponatinib. There is a general consensus that patients who fail after imatinib should change without hesitation to either nilotinib or dasatinib. The choice should be guided by the mutation profile, if relevant, the comorbidities of the patient, the side effects of the drugs, and the availability of the drugs. The presence of BCR-ABL mutations is a way to guide to which one of TKIs should the clinician choose as a second-line treatment after Imatinib failure. Direct sequencing of DNA after qRT-PCR is most often used by clinicians to identify specific mutations in the BCR-ABL kinase domain. In a survey of BCR-ABL mutations in 386 CML subjects, Branford and colleagues identified specific mutations, which conferred significant resistance to nilotinib (E255K/V, Y253H, and F359C/V) and dasatinib (V299L and F317L). Ponatinib is the only approved TKI that binds to the T315I BCR-ABL mutant protein.[11-15]

CONCLUSION

Treatment monitoring in CML management is very important. The presence of ACAs is a sign of disease progression and poor prognosis. We need to properly decide when to change to alternative therapy based on hematology, molecular and cytogenetic testing.

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