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CASE REPORT

Mechanism of resistance to tyrosine kinase inhibitors - A case report and review

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ABSTRACT

This report aims to assess the viability of various challenging approaches such as tyrosine kinase inhibitors (TKIs) therapy, chemotherapy, and stem cell transplantation in patients with chronic myeloid leukemia (CML), especially for those in an advanced phase. Although standard treatments have been extremely effective in combating CML propagation and negating the disease symptoms along with an increased survival rate, these traditional treatment methods have experienced an increased failure rate due to TKI treatment resistance. A common mechanism that can be attributed to the increase in TKI resistance is the increasing mutations of the BCR-ABL 1 kinase domain. These mutations can be clearly observed in clinical trials. Currently, there are five BCR-ABL 1 kinase inhibitors that are approved for the safe treatment of CML. These are imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. Mutational testing should be carried out on patients in such cases that show little response to traditional TKI therapy.In this report, we evaluate a patient who has been diagnosed with an accelerated phase CML and requires constant monitoring to tailor the treatment program to their requirements.

KEY WORDS: BCR-ABL; Chronic Myeloid Leukemia; Tyrosine Kinase Inhibitors; Imatinib

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) are considered as a turning point in the CML therapeutic landscape. Since their introduction as a viable TKI against BCR-ABL 1 kinase, there has an observable improvement in the clinical outcome of chronic myeloid leukemia (CML) patients and so have become common place in the area of CML treatment, along with long-term stability for most patients. Its not complete smooth sailing, however, as a proportion of CML patients have experienced either primary or secondary form of resistance to imatinib.[1]

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It has been found that the most likely cause for the resistance to imatinib found in a proportion of patients can be linked to point mutation in the BCR-ABL kinase domain. Roughly, 90 point mutations are known to be causing this resistance. Nilotinib, dasatinib, and bosutinib are some prominent examples of second generation TKIs and ponatinib are an example of a third generation of TKI. New generation TKIs have been developed, but these also have their own adverse effects and patients have been seen to develop resistance to these drugs as well.[1]

Patients diagnosed with accelerated and blast phase of CML has a bad response while treatment only using TKIs. Such patients are required to undergo a combination of chemotherapy with bone marrow transplantation procedures for betterment of results. Close monitoring of the clinical condition of the patient is also mandatory.[1]

A guideline report by the National comprehensive cancer network clinical practice in oncology (NCCN Guidelines)

for CML provides therapeutic options based on BCR-ABL 1 kinase domain mutation status. However, they only create standard recommendations for the assessment of the patients who are resistant to TKI therapy.[2]

Therapeutic management of CML patients range from chemotherapy to BCR-ABL mutation guided TKI therapy to stem cell transplantation. In the following section, we explore the case of a patient who has been diagnosed with accelerated phase CML who was diagnosed with BCR-ABL mutation. We also outline the treatment options available for CML patients.

CASE REPORT

A 46-year-old female was diagnosed to have CML-accelerated phase in June 2013 from outside hospital. The patient had no past medical history. BCR-ABL was positive which was assessed by imatinib resistance mutation analysis (qualitative). This assay is based on nested RTPCR and Sanger sequencing. Bone marrow biopsy was not done. The patient was started on imatinib 400 mg OD. In August 2016, patient had severe bone pains, and platelets counts were elevated to 13 K/uL. Imatinib dose was increased to 600 mg OD. The patient had complaints of pain over lower limb for the past 3 months for which she was admitted to our hospital for further evaluation and treatment. Routine laboratory investigations, bone marrow aspiration and biopsy were carried out. Aspiration showed hypercellular marrow with megakaryocytic hyperplasia, increase in eosinophils (12.00%), and basophils (20.00%). No increases in blasts were seen. As she had uncontrolled thrombocytosis and she was diagnosed to have CML in accelerated phase. Biopsy revealed hypercellular marrow showing myeloid predominance, increase in eosinophils, and precursors along with megakaryocytic hyperplasia. BCR/ABL RT-PCR detected BCR-ABL1/ABL1% ratio: 84. 32180. As the platelets were persistently elevated, an imatinib resistance mutation test was done. Y 253 H mutation was detected in the p-loop domain of BCR-ABL 1 transcript. This is a clinically relevant mutation and has been previously reported in patients who develop resistance to imatinib. The mutant clone comprises 100% of the BCR-ABL 1 transcript load. The patient was started on capsule hydroxyurea 500 mg BD from 2/11/2016. Mild fever spikes were noted during the hospital stay. Laboratory investigations also revealed neutropenia. The cultures were sterile and patient was started emperically on iv antibiotics, growth factors and supportive measures. The patient was then started with Dasatinib 70 mg BD. Now she is symptomatically better, and she is on follow-up.

DISCUSSION

It is evident that clinical management of patients suffering from CML has been radically reformed, especially since the introduction of TKIs to inhibit BCR-ABL. As TKI therapy has been proven to be effective, after careful review of patient condition, there are a range of first and second generation TKIs that can be administered to the patient depending on cost and availability.[1]

Although effective, some patients can form partial or complete resistance to TKI therapy. We explore the mechanisms behind resistance to TKIs in a patient with accelerated phase CML and its management. According to the WHO, accelerated phase CML is defined as blast 10-19% of white blood cells in peripheral and or nucleated bone marrow cells; persistent thrombocytopenia($<100 \times 10^9$/L) unrelated to therapy or persistent thrombocytosis($>1000 \times 10^9$/L) unresponsive to therapy; increasing white blood cells and spleen size unresponsive to therapy; cytogenetic evidence of clonal evolution.

Common mechanisms of resistance include point mutation, deletion and amplification of genomic areas, drug efflux or influx, etc. Frequent mutation types are found to be those that reduce the drug affinity for the target kinase domain. Rapidly dividing cancerous cells are found to be the source of mutation as point mutations are the most common TKI resistance mechanism. Study of patients medicated with imatinib showed that small TKI bound with more affinity to c-abl kinase.[3] The FDA approved imatinib for public use in 2001. Mutation of Y 253H allows for the amino acid substitution at position 253 in BCR-ABL 1 from tyrosine (Y) to a histidine (H). The presence of such mutation has been regarded as the mechanism for imatinib resistance.

Similarly, the previous example, dasatinib and nilotinib were also approved by the FDA for use in the clinical management of CML. Y253H mutated cells showed reduced sensitivity to nilotinib during pre-clinical trials and similarly for dasatinib relative to CML wild cell line mutation types. Hence, it was recommended to use dasatinib rather than nilotinib alternative when administering to CML patients that showcase imatinib resistance.[4]

One of the major mechanisms of oncogenic activation is gene amplification. It can also produce resistance to treatment through amplification of genes that encodes for key transducers driving signaling pathways that can compensate for the signals lost due to target inhibition. It is found that there is a correlation between activating mutations in kinase domain or gene amplification and response to TKIs which is evident from other clinical studies. Another mechanism implicated in causing lack of response to treatment is the reduction of drug intracellular concentration. Drug efflux or influx and drug plasma sequestration are the most important resistance mechanisms. In cancer patients, the incidence of multidrug resistance is a frequent cause of treatment failure. Another common cause is development of stuff resistance and genomic alterations like deletions.[3]

Close monitoring of the patient using cytogenic analysis, preferably molecular test for BCR-ABL is very important in managing and understanding treatment response of patients with CML, as the response to treatment is the most important prognostic factor and should guide individual treatment. Patients need to be monitored every 3 months but in the case of serious patients monitoring need to be done every month.[1,5] Even though our patient was tested positive for BCR-ABL mutations, it is not known whether the mutation developed initially or after treatment with TKIs. Earlier detection of specific mutations might have prompted immediate new generation TKI therapy. While second generation, TKIs s such as dasatinib showed activity in Y253H mutated CML and bosutinib was found to be active in E255K mutated CML, only third generation TKIs ponatinib was active against T315I mutated CML[1,6] and we chose dasatinib 70 mg OD.

CONCLUSION

Newer laboratory and clinical studies have found that multitargeting approaches against neoplastic cells can help increase the survival of the patient, and thus, reduce the emergence of cell resistant to single target inhibitors.[3] Hence, summarizing on a patient with CML accelerated phase, who was treated with chemotherapy, sequential TKIs, this case illuminates major challenges faced in treating CML patients and emphasize the need for modification in therapies individually in accordance with thorough monitoring of response in treatment plans. Monitoring must be deployed every 3 months but done on monthly basis for patients who are more serious.[1]

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