Chronic Myeloid Leukaemia with Extreme Thrombocytosis and T315I BCR-ABL Kinase Domain Mutation: A Case Report

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ABSTRACT

Thrombocytosis is a common feature of myeloproliferative neoplasms, including Philadelphia chromosome-positive chronic myeloid leukaemia. However, symptomatic extreme thrombocytosis causing thrombotic and/or haemorrhagic events is uncommon during the chronic phase of chronic myeloid leukaemia, especially when compared to Philadelphia chromosome-negative myeloproliferative neoplasms like polycythemia vera and essential thrombocythemia. We report a case of chronic myeloid leukaemia with a complicated clinical course. The patient did not show a molecular response to imatinib, a tyrosine kinase inhibitor, and was eventually admitted to the hematology/oncology department of King Hussein Medical Center with extreme thrombocytosis, prompting urgent plateletpheresis. Upon further investigation, molecular analysis to search for ABL kinase domain mutations revealed a positive result for the T315I mutation, explaining the resistance to treatment and disease progression.

Key words: Chronic myeloid leukemia; Extreme thrombocytosis; Tyrosine kinase inhibitor resistance; T315I mutation; Plateletpheresis

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Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm (MPN) which accounts for 15–20% of all cases of adult leukaemia.[1] It is characterised by a genetic translocation t(9;22) which involves a fusion of the ABL1 gene on chromosome 9q34 with the BCR gene on chromosome 22q11.2. This forms the BCR-ABL fusion gene on the Philadelphia chromosome, which encodes a continuously activated non-receptor tyrosine kinase, resulting in uninhibited haematopoietic proliferation.[2-4]

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Patients diagnosed with this entity typically present with constitutional symptoms, anaemia and splenomegaly.Approximately 50% of patients are asymptomatic, and CML is discovered by an accidental reading of a high white cell count.[5] Tyrosine kinase inhibitors (TKI) have revolutionised the therapeutic approach to CML. This is evident by an improvement in the 10-year survival rate from 20% to 80–90% with the first generation TKI, imatinib.[6] Second and third generation TKIs have shown even higher potency in many studies.[7-10] Response to treatment is best monitored by reverse transcription polymerase chain reaction (RT-PCR) of peripheral blood samples.[11,12] Certain point mutations in the BCR-ABL kinase domain (KD) that confer resistance to one or more TKIs have been identified, and these mutations are associated with disease progression.[13-15]

We report a case of CML with extreme thrombocytosis, positive T315I mutation and resistance to multiple TKI treatments.

Case Report

We present the case of a 46-year-old female patient who was diagnosed with CML in the chronic phase in February 2015 with a platelet count of $800\times10^3/\mu L$. At the time of diagnosis, she had a low Sokal score of 0.7 and 95% positivity for the BCR-ABL fusion gene by fluorescence in situ hybridisation (FISH).

Frontline treatment with imatinib (400 mg) was initiated. In the beginning, a good response to treatment was evident as both haematological and cytogenetic responses were achieved. However, the patient had not achieved a molecular response as her RT-PCR result for the BCR-ABL fusion gene was never less than 2.7% over a 3-year follow-up period.

The dose of imatinib was increased to 600 mg, but the RT-PCR value increased to 25% in July 2018. At this point, a second-line treatment was considered, and the patient was switched to nilotinib at a dose of 400 mg twice daily. In her next visit to the clinic the following month, she complained of headache. A complete blood count revealed a very high platelet count of $4465 \times 10^3/\mu L$, which was confirmed by a peripheral blood smear (Figure 1).

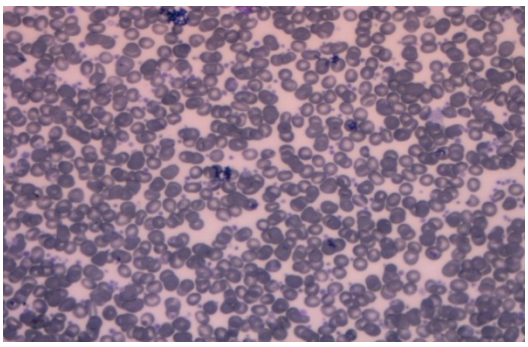

Figure 1. Peripheral blood smear showing extreme thrombocytosis.

The patient was immediately admitted to the hospital and started on hydroxyurea at a dose of 1 g twice daily, in addition to mechanical removal of platelets by plateletpheresis as a prophylactic measure. She underwent four sessions of platelet depletion using the Spectra Optia Apheresis System, lowering her platelet count to $1600 \times 10^3/\mu L$ without any complication such as bleeding or hypocalcaemia. This was achieved over a period of 1 week, during which further investigations were carried out. Bone marrow study revealed granulocytic hyperplasia and marked megakaryocytic hyperplasia (Figure 2). FISH study showed positivity for the BCR-ABL fusion gene in 45% of cells. The diagnosis of CML in the accelerated phase was made according to the latest revision of the World Health Organization's classification of myeloid neoplasms.[16]

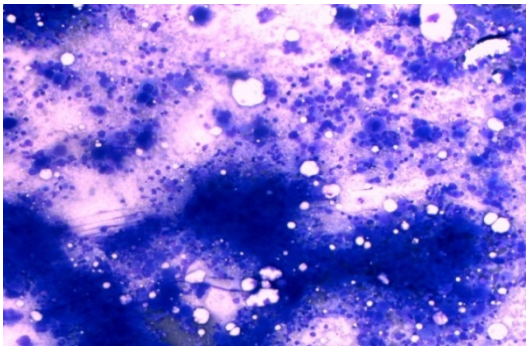

Figure 2. Bone marrow aspirate showing hypercellularity and a marked increase in megakaryopoiesis with micro-mononuclear (dwarf) forms.

The persistent finding of unresponsive extreme thrombocytosis merited further investigation, including JAK2 V617F, CALR , MPL and p-STAT5 mutations. Unfortunately, testing for only the first mutation was available, which revealed a negative result. A blood sample was sent to the hemostasis and thrombosis laboratory at Jordan University Hospital to look for BCR-ABL KD mutations. The result was positive for the T315I "gatekeeper" mutation. Ponatinib, a third generation TKI, is the drug of choice in such cases. However, at that time it was unavailable in Jordan, so the patient was started on a second generation TKI, dasatinib, at a dose of 100 mg per day. The dosage was reduced to 70 mg due to haematologic toxicity (anaemia and neutropenia), in addition to headache.

During regular follow-up at our hematology/oncology clinic in King Hussein Medical Center, the patient reported compliance to her medications, with no symptoms and no side-effects from the drug. The most recent hemogram performed in October 2019 revealed haematological response with a normal white cell count, as well as a normal platelet count of $308 \times 10^3/\mu L$. However, cytogenetic and molecular responses were not achieved, as her BCR-ABL levels assessed by FISH and RT-PCR were still 10% and 1.2%, respectively. The patient is planned to switch to ponatinib once it becomes available at our centre.

Discussion

The first generation TKI, imatinib, revolutionised the therapeutic approach to CML, evidenced by the decreased annual mortality rate of CML from 10–20% to 1–2%.[17]

Response to treatment is measured on three levels: hematologic, cytogenetic, and molecular. The molecular response has the greatest sensitivity for response monitoring, and is quantified by RT-PCR. A major molecular response is achieved when *BCR-ABL falls to ≤0.1%.*[12] Our patient did not achieve a molecular response to imatinib, so was switched to nilotinib as a second-line treatment, after which her disease progressed to an accelerated phase with extreme thrombocytosis and a very high platelet count of $4465 \times 10^3/\mu L$. Disease progression despite second-line TKI treatment raised the possibility of additional genetic abnormalities. Therefore, BCR-ABL KD mutation analysis was performed, which revealed the presence of the T315I mutation.

In the era of TKIs, at least one in four patients will change TKI at least once due to intolerance or an inadequate response, i.e., drug resistance.[11,14] Many point mutations in the BCR-ABL KD have been found to confer variable degrees of resistance.[11-15] The most resistant among these is the T315I mutation, which is resistant to all of the currently approved TKIs except for ponatinib, the drug of choice for these patients.[10,12] Unfortunately, we were unable to provide our patient with this drug at that time because it remained unavailable in Jordan.

Thrombocytosis is a poor prognostic factor of CML as it is associated with shorter survival.[18] Thrombocytosis of more than $500 \times 10^3/\mu L$ was reported by Jameel and Jamil in 10% of CML cases.[19] However, extreme thrombocytosis exceeding $1000 \times 10^3/\mu L$ is uncommon in CML, but is typical of Philadelphia chromosome-negative essential thrombocythemia (ET). Our patient had an extremely high platelet count higher than $4000 \times 10^3/\mu L$, which is rarely reported in the literature. Thus, an important differential diagnosis arose for our patient, which is reported in the literature as Philadelphia chromosome-positive ET.[20,21] This entity was ruled out by the presence of features of CML in the peripheral blood and bone marrow in our case, which are typically absent in such ET cases. Also, molecular analysis for the JAK2 V617F mutation was performed, which revealed a negative result. Unfortunately, molecular studies for CALR, MPL and p-STAT5 mutations were not available.

Symptomatic extreme thrombocytosis is rarely described in CML case reports; however, the few available cases describe digital ischemia,[22,23] myocardial infarction[24] and neurologic symptoms such as uneasiness and headache, similar to our patient.[22]

According to Sora et al. and Liu Z, extreme thrombocytosis is more commonly seen in female CML patients, as seen here, with a median age of 59 years and high Sokal scores.[25,26]

Many studies explored different molecular mechanisms that result in the extreme thrombocytosis seen in CML patients. Lewandowski et al. found in their study that TKI-treated CML patients with thrombocytosis and positive JAK2 V617F or CALR mutation did not reach complete hematologic response due to the persistence of thrombocytosis. [27] Turakhia et al. found that p-STAT5 expression was activated in 85.7% of their CML patients with thrombocytosis. [28] Overexpression of EV11 gene was linked to extreme thrombocytosis in a reported case of CML.[29]

This rare case of CML highlights the importance of assessing the ABL KD mutation status and related molecular studies in cases that fail to respond to treatment. Determining the mutation

profile of such patients is essential to provide the best and most cost-effective management, in addition to avoiding complications and disease progression, and prolonging event-free survival.

Abbreviations:

BCR-ABL KD	BCR-ABL kinase domain
CML	Chronic myeloid leukaemia
FISH	Fluorescence in situ hybridisation
MPN	Myeloproliferative neoplasm
RT-PCR	Reverse transcription polymerase chain reaction
TKI	Tyrosine kinase inhibitor

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