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Case Report

Late Emergence of an Imatinib-Resistant *ABL1* Kinase Domain Mutation in a Patient with Chronic Myeloid Leukemia

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The introduction of the tyrosine kinase inhibitor (TKI) imatinib has revolutionised the outlook of chronic myeloid leukemia (CML); however, a significant proportion of patients develop resistance through several mechanisms, of which acquisition of *ABL1* kinase domain mutations is prevalent. In chronic-phase patients, these mutations become evident early in the disease course. A case is described of a chronic-phase CML patient who achieved a sustained, deep molecular response but who developed an Y253H *ABL1* kinase domain mutation nearly nine years after commencing imatinib. Switching therapy to bosutinib resulted in a rapid reachievement of a major molecular response. Long-term TKI treatment impacts on quality of life and late losses of responses are usually due to lack of adherence. This case highlights the requirement for *ABL1* kinase domain mutation analysis in those CML patients on long-term imatinib who lost their molecular response, regardless of whether nonadherence is suspected.

1. Introduction

Introduction of the tyrosine kinase inhibitor (TKI) imatinib has revolutionised the treatment of patients with chronic myeloid leukemia (CML) with long-term administration showing persistent efficacy and lack of unacceptable cumulative or late toxic effects [1]. Resistance to imatinib, either primary or acquired, is a recurrent problem in a significant proportion of CML patients that have been largely abrogated by the development and introduction of second- and third-generation TKIs [2]. One of the major causes of imatinib resistance is the development of *BCR-ABL1*-positive clones harboring mutations within the *ABL1* kinase domain (KD) with identification of these mutations as important in selecting a subsequent TKI [3]. Studies have shown that, in newly diagnosed, chronic-phase CML patients, *ABL1* KD mutations predominantly manifest within eighteen months of commencing imatinib and usually in those patients whose best response has only been hematological or cytogenetic [4, 5]. Evidence exists for both increased and low rates of *ABL1* KD mutations in late as opposed to early chronic-phase patients [6, 7]. A CML patient is described in whom an *ABL1* KD mutation was detected nearly nine years after starting imatinib and who had previously achieved a sustained and deep molecular response.

2. Case Report

A 49-year-old female presented with nausea, vomiting, and weight loss. Full blood count revealed a white blood cell count of 238.0×10^9/L, hemoglobin of 7.7 g/dL, and platelets of 746×10^9/L. Bone marrow morphology revealed granulocytic hyperplasia with increased megakaryocytes and <1% myeloblasts. Cytogenetics detected the t(9;22) translocation with molecular analysis demonstrating high levels of e13a2 *BCR-ABL1* transcripts, consistent with a diagnosis of chronic-phase CML with a low-risk Sokal score. She commenced imatinib 400 mg oral daily with transient toxicities of nausea and increased susceptibility to infections but overall tolerated imatinib well, achieving a major molecular response (MMR) of *BCR-ABL1*/*ABL1* 0.09% on the International Scale (IS) at

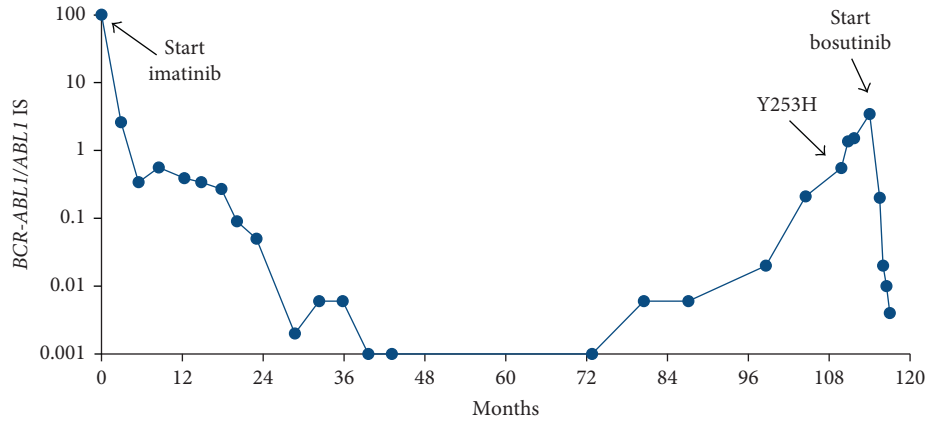

Figure 1: *BCR-ABL1* transcript levels throughout clinical course.

20 months (Figure 1). *BCR-ABL1* transcripts became undetectable (<0.001% IS) at 40 months with optimal adherence and a good quality of life. After *BCR-ABL1* transcripts became undetectable, monitoring intervals were extended to six months. Rising transcript levels resulted in loss of MMR at 105 months, peaking at a *BCR-ABL1/ABL1* IS of 3.43%, almost nine years after starting imatinib (Figure 1). After adherence was assured, *ABL1* KD mutation analysis was performed as previously described [3, 8] and detected the Y253H (c.757T > C; NM_005157.5) mutation. The time between loss of MMR and mutation detection was six months. The patient then switched to bosutinib 500 mg oral daily [9], reduced to 400 mg oral daily after gastrointestinal toxicities, which resulted in an MMR within three months (*BCR-ABL1/ABL1* IS 0.02%). The *BCR-ABL1* transcript level continues to decline (Figure 1) with continued frequent monitoring advocated.

3. Discussion

The long-term mild and chronic side effects of TKI therapy may impact on quality of life of CML patients and could be a trigger for lack of adherence [10]. Despite a minor delay in achieving an MMR [11], this patient maintained a sustained molecular response for a significant period of time. *ABL1* kinase domain mutation analysis provided the rationale for switching TKI to bosutinib which induced a rapid molecular response. This case suggests that loss of MMR should always trigger *ABL1* KD mutation analysis even after many years of follow-up, regardless of whether nonadherence is suspected.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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