Case Report

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

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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
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.

References


