SUBOPTIMAL MOLECULAR RESPONSE TO TYROSINE KINASE
INHIBITION ASSOCIATED WITH ACQUISITION
OF A T240A ABL1 KINASE DOMAIN MUTATION IN A PATIENT
WITH CHRONIC MYELOID LEUKEMIA

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Over the last twenty years, chronic myeloid leukemia (CML) has come to be considered a paradigm for rationally selected, targeted inhibition of the disease-specific, BCR-ABL1 tyrosine kinase activity. However, a minor but significant numbers of patients either fail, or have suboptimal responses to first line tyrosine kinase inhibitor (TKI) therapy. The causes of a suboptimal response are many, with the acquisition of ABL1 kinase domain mutations (KDMs) contributing to resistance being widely studied. These ABL1 KDMs usually become apparent within the first two years of starting TKI therapy and their discovery has led to the development of second and third generation TKIs [1]. ABL1 KDMs have been detected throughout the kinase domain with ten common mutations accounting for the majority of those observed [2]. However, rare and novel mutations continue to be detected in TKI-resistant patients with reporting of such cases necessary for future understanding of real-world CML patient management [3].

A 44 year-old man presented with fatigue, weight loss, night sweats, abdominal discomfort, and a hemoglobin of 9.9 g/dl, white cell count of 353.9·10^9/l and platelet count of 130·10^9/l. The patient had a marked splenomegaly detected 17 cm below the costal margin. Bone marrow aspirate showed hypercellularity, myeloid metaplasia, only 1% basophils and no myeloblasts with cytogenetics detecting the t(9;22) translocation in all metaphases analysed. Quantitative reverse-transcription polymerase chain reaction detected e13a2 BCR-ABL1 transcripts at a high level, all consistent with a diagnosis of high-risk (Sokal score 1.5; EUTOS score 88), chronic phase CML. The patient commenced nilotinib 300 mg twice daily with BCR-ABL1 transcript levels decreasing very slowly (Figure). Within the first year of treatment he experienced intermittent eye irritation, conjunctival hyperemia which required occasional steroid eye drops and ocular lubricant, and a persistent sensation of asthenia with regular myalgias. His peripheral blood BCR-ABL1 transcript level (Internationally Standardised) at twelve months was a suboptimal 4.87% prompting switch to dasatinib 100 mg once daily increased to 140 mg once daily. At twenty months post-diagnosis, the BCR-ABL1 transcript level was 2.12% triggering analysis for an ABL1 KDM as previously described [4] and of which no mutation was detected (Figure). Despite a continued slow decline in BCR-ABL1 transcripts, a major molecular response was never achieved with re-analysis for an ABL1 KDM at 47 months detecting an ABL1 T240A mutation (c.718A>G, p.Thr240Ala; reference sequence NM_005157.5). The patient is currently well with persistent thrombocytopenia secondary to dasatinib and occasional myalgias. He continues attending for regular close molecular monitoring with a most recent BCR-ABL1 level of 0.15% five years post diagnosis.

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Abbreviations used: CML – chronic myeloid leukemia; KDM – kinase domain mutations; TKI – tyrosine kinase inhibitor.

Figure. BCR-ABL1 transcript levels throughout disease course

To date, real-world evidence of the degree of TKI resistance conferred by acquisition of the ABL1 KDM T240A has been unclear: this mutation has been previously described once in highly selected CML stem cells cultured in vitro and once at a low level in a CML patient with multiple other mutations during second line dasatinib therapy [5, 6]. The case reported herein provides evidence for acquisition of the T240A mutation to contribute to a sub-optimal molecular response in a patient with chronic phase CML. Whether the T240A mutation was present at a level below the detection sensitivity of Sanger sequencing at 20 months is not known. The introduction of next-generation, deep-sequencing approaches are likely to improve ABL1 KDM detection allowing a timelier re-consideration of TKI therapy [7].

CONFLICTS OF INTEREST

The authors declare no competing financial interests.
REFERENCES


