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LETTER TO EDITOR

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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 $353.9 \cdot 10^9$/l and platelet count of $130 \cdot 10^9$/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.

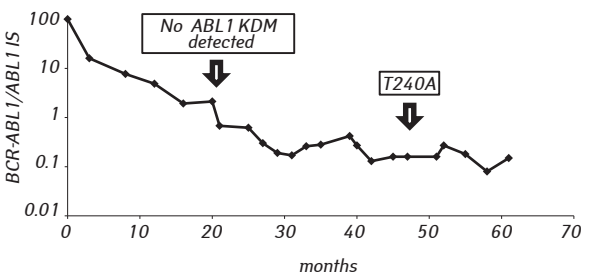

Figure. *BCR-ABL1* transcript levels throughout disease course

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.

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

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