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LETTER TO EDITOR

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FREQUENCY AND SPECTRUM OF ATYPICAL *BCR-ABL1* TRANSCRIPTS IN CHRONIC MYELOID LEUKEMIA

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The *BCR-ABL1* oncogene is the molecular hallmark of chronic myeloid leukemia (CML) with the majority of patients possessing a fusion between *BCR* exon 13 or 14 and *ABL1* exon a2 (e13a2 and e14a2 respectively). However, a minority of patients express atypical transcripts usually as due to splicing of alternative *BCR* or *ABL1* exons. These variants become apparent upon discordant diagnostic cytogenetic and molecular testing and may be resolved by multiplex, reverse transcription polymerase chain reaction (RT-PCR) or sequencing approaches [1]. In a recent international survey of *BCR-ABL1* transcript types in more than 34,000 CML patients, 1.93% of cases expressed these atypical forms [2]. It is therefore likely that any laboratory performing molecular diagnosis or monitoring of more than 50 CML patients will have encountered a variant *BCR-ABL1* transcript. We sought to review the incidence and type of atypical *BCR-ABL1* transcripts in CML patients from the National molecular diagnostic centre in order to inform appropriate diagnostic and monitoring techniques.

New or existing CML patients were identified from January 2005 to June to 2019 inclusive at the National center for the molecular diagnosis and monitoring of CML in Ireland. All patients had cytogenetic or fluorescence *in situ* hybridization confirmation of a t(9;22) translocation or *BCR-ABL1* fusion signal respectively. *BCR-ABL1* detection and quantitative RT-PCR were performed using standardized approaches throughout this period with Sanger sequencing used for confirmation of an atypical fusion transcript [3, 4]. Of 706 CML patients, atypical *BCR-ABL1* transcripts were detected in 16 (2.3%). These variants comprised e1a2 (n = 4), e6a2 (n = 2), e8a1 (n = 1), e13a3 (n = 1), atypical e13a2 with a deletion and insertion (n = 2), and e19a2 (n = 6).

The above demonstrates that the frequency and spectrum of atypical *BCR-ABL1* transcripts in the Irish CML population is similar to that seen elsewhere. The clinical importance of correct identification of the atypical *BCR-ABL1* transcripts is two-fold. Firstly, there is accumulating evidence for a *BCR-ABL1* genotype-tyrosine kinase inhibitor (TKI) response correlation: patients expressing the shorter transcript types such as e1a2 and e6a2 have an aggressive disease with higher rates of blast crisis transformation [5, 6] whereas TKI responses in patients with longer *BCR-ABL1* transcript types such as the e19a2 are generally favorable [7, 8]: establishing the transcript type will therefore inform selection of TKI. Secondly, monitoring the molecular response by quantitation of *BCR-ABL1* transcripts is now an integral part of CML patient management with significant advances made towards harmonization of different methodological approaches: characterization of a variant transcript type therefore allows selection of correct primers and probes for quantitative RT-PCR. However, to date, quantitation of atypical *BCR-ABL1* transcript has only been performed on an *ad hoc* basis [9]. Given that the survival of CML patients receiving TKI therapy is similar to that of the normal population, more patients with these atypical *BCR-ABL1* transcripts will require monitoring. Furthermore, given the possibility for treatment-free remission in which important criteria for TKI discontinuation are the length and depth of molecular remission, consensus standards and methodologies are now required for this small but expanding population of CML patients.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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Abbreviations used: CML – chronic myeloid leukemia; RT-PCR – reverse transcription polymerase chain reaction; TKI – tyrosine kinase inhibitor.

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