

LETTER TO THE EDITOR

Molecular Responses in Chronic Myeloid Leukemia with Atypical BCR-ABL1 Transcripts: Is Digital PCR the Answer?

Stephen E. Langabeer¹, PhD, FRCPath

¹ Cancer Molecular Diagnostics, St. James's Hospital, Dublin, Ireland.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Correspondence to: Stephen E. Langabeer, Cancer Molecular Diagnostics, Trinity Translational Medicine Institute, St. James's Hospital, Dublin, D08 W9RT, Ireland.

Email: slangabeer@stjames.ie

Telephone: +353 14162413

Received: October 13, 2020

Revised: November 10, 2020

Accepted: November 16, 2020

Published online: November 19, 2020

ABSTRACT

Serial monitoring of the level of *BCR-ABL1* transcripts is an integral part of chronic myeloid leukemia (CML) management. However, assay standardization is lacking for those patients who express atypical *BCR-ABL1* transcripts. Given the increasing survival number of CML patients and the option of treatment-free remission, quantitation of atypical transcripts by digital PCR is emerging as an attractive alternative to real-time quantitative PCR in such patients.

Key words: Chronic myeloid leukemia; *BCR-ABL1*; Molecular response; Atypical transcripts; Treatment-free remission

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Langabeer SE. Molecular Responses in Chronic Myeloid Leukemia with Atypical *BCR-ABL1* Transcripts: Is Digital PCR the Answer?

International Journal of Hematology Research 2020; 5(1): 191-192
Available from: URL: <http://www.ghrnet.org/index.php/ijhr/article/view/3008>

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In the last twenty years, chronic myeloid leukemia (CML) has become the paradigm for a malignancy targeted by rationally-designed tyrosine kinase inhibitors (TKI): overall survival of patients is now similar to individuals without the disease^[1]. Furthermore, adhering to judicious criteria, TKI may be discontinued in selected CML patients with approximately half achieving and maintaining a treatment-free remission (TFR)^[2]. Monitoring expressed *BCR-ABL1* fusion transcripts, the molecular hallmark of CML, by real-time quantitative PCR (RT-qPCR) has become an integral part of patient management with international guidelines setting molecular milestones for optimal therapeutic outcome. Considerable global efforts have resulted in the harmonization of individual laboratory RT-qPCR assays with the widespread ability to report *BCR-ABL1* responses on a standardized international scale^[3]. While most CML patients express e13a2 or e14a2 *BCR-ABL1* transcripts, a minority of approximately 2% of patients express uncommon *BCR-ABL1* transcripts, usually due to alternative splicing of *BCR* or *ABL1* exons^[4]. However, the aforementioned efforts for harmonising molecular responses in CML applies only to those patients expressing the common variants with little or no harmonization of *BCR-ABL1* RT-qPCR assays for these atypical standards. There remains a growing and unmet need to detect deep molecular responses in a standardized fashion for those patients harbouring the atypical *BCR-ABL1* transcript types.

A recent advance in this area is the increasing use of digital PCR (dPCR). Advantages of dPCR are reported to be an increase in the detection limit achieved by partitioning the sample in thousands of independent PCR reactions increasing the effective concentration, that dPCR is less prone to variations in amplification efficiency by measuring the end point of amplification, and the lack of requirement for a calibrated standard curve enabling absolute quantification of target molecules^[5]. Several studies have shown the applicability of dPCR in measuring the common *BCR-ABL1* transcripts in CML patients with a similar, if not an improved sensitivity over RT-qPCR, in measuring deep molecular responses and predicting TFR^[6]. However, it is monitoring those patients expressing the rare, variant *BCR-ABL1* transcript types in which dPCR may be the most beneficial due to the current lack of standardization. Proof of principle for this approach

came by measuring e6a2 *BCR-ABL1* transcripts in a patient with blast phase CML^[7]. This has been followed by a more recent study showing the usefulness of digital PCR in following CML patients expressing e13a3, e14a3 and e19a2 *BCR-ABL1* transcripts^[8]. This observation has been successfully expanded to encompass *BCR-ABL1* monitoring by dPCR during TFR attempts^[9].

While traditional RT-qPCR remains an option for monitoring the rare *BCR-ABL1* transcript types, the lack of methodological harmonization, the increasing number and overall survival of CML patients that require monitoring, and the possibility of attempting TFR, all contribute to the appeal and potential expanding role of a dPCR approach for monitoring CML patients with the atypical *BCR-ABL1* transcript types in the future.

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