Irish Journal of Medical Science (1971 -) (2019) 188:351–352
https://doi.org/10.1007/s11845-018-1838-6

LETTER TO THE EDITOR

The impact of sample processing delay on deep molecular responses in chronic myeloid leukemia

Stephen E. Langabeer[1] · Mireille Crampe[1] · Tara Durney[1]

Received: 13 April 2018 / Accepted: 31 May 2018 / Published online: 6 June 2018

Dear Sir,

Molecular monitoring the expression of *BCR-ABL1* transcripts, resulting from the formation of the Philadelphia chromosome by the t(9;22) translocation, has become an integral part of the modern management of patients with chronic myeloid leukemia (CML) in the era of tyrosine kinase inhibitors (TKI). Residual disease assessment is performed by simultaneous quantitative reverse-transcription polymerase chain reaction (qRT-PCR) of *BCR-ABL1* and control gene transcripts derived from ribonucleic acid (RNA) extracted from patient peripheral blood samples. Early and prolonged molecular responses not only determine progression-free and overall survival, but precise and consistently measured, deep molecular remissions can be used to guide which patients are eligible for stopping TKI, enabling an impressive treatment-free remission (TFR) [1]. One of the major variables in the standardized measurement of these deep molecular responses is the quantity and quality of the RNA sample as determined by the level of control gene transcripts, with the deep molecular response of $MR^{4.5}$ and MR^{5} requiring a minimum of 32,000 and 100,000 *ABL1* control gene transcripts respectively [2]. It is generally accepted that RNA degrades over time without stabilization: guidelines suggest that sample preparation should occur no longer than 48 h after take [3]. However, the impact of delay on sample quality and the subsequent ability to measure deep *BCR-ABL1* responses has not been assessed in a real-world situation by this center due to the precious nature of the clinical material. The arrival of Storm Emma in the Republic of Ireland in early 2018 afforded an opportunity to address this question.

Storm Emma tracked northwards over Ireland with its associated frontal systems yielding widespread snow, ice, and low temperatures culminating in Met Éireann issuing a "Status Red-Severe Weather Warning" for the three normal working days of Wednesday 28 February to Friday 2 March 2018 [4]. This resulted in a subsequent delay of transportation and processing of samples for *BCR-ABL1* analysis to a central laboratory. All delayed samples were processed the following week regardless of sample age by a standardized approach, and all passed the criterion for sample quality acceptance (> 10,000 *ABL1* control transcripts) [3]. Samples delayed for more than 3 days ($n = 7$; median delay 5 days) had a mean *ABL1* control gene level of 94,386 transcripts. Samples received the same week and processed within 48 h using the same batches of qRT-PCR reagents ($n = 14$) had a noticeably higher mean *ABL1* control gene level of 134,671 transcripts.

Acknowledging the restricted sample numbers, a difference in the ability to distinguish between standardized levels of deep molecular response in CML patients is evident between new and aged samples. As the possibility of achieving TFR is becoming an increasingly important question in CML, these findings may impact on the decision of eligibility for cessation of TKI therapy. This informative observation therefore emphasizes the requirement for prompt dispatch and processing of peripheral blood samples for molecular monitoring of *BCR-ABL1* levels in CML patients.

Compliance with ethical standards

This study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from participants at the referring centers.

Conflict of interest The authors declare that they have no conflicts of interest.

✉ Stephen E. Langabeer
slangabeer@stjames.ie

[1] Cancer Molecular Diagnostics, Central Pathology Laboratory, St. James's Hospital, Dublin D08 E9P6, Ireland

References

1. Branford S (2016) Molecular monitoring in chronic myeloid leukemia—how low can you go? Hematol Am Soc Hematol Educ Program 2016:156–163
2. Cross NC, White HE, Colomer D et al (2015) Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. Leukemia 29:999–1003
3. Foroni L, Wilson G, Gerrard G et al (2013) Guidelines for the measurement of BCR-ABL1 transcripts in chronic myeloid leukaemia. Br J Haematol 153:179–190
4. www.met.ie. Accessed 11th April 2018