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Initial Rate of *BCR::ABL1* Decline for Response Prediction in Chronic Myeloid Leukemia

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In this issue of the journal, Ceran et al. confirm the importance of the initial rate of *BCR*::*ABL1* transcript decline as a prognostic indicator in a cohort of 40 first-line imatinib treated patients.[1] Patients with the most rapid reductions, which were assessed as the number of days over which *BCR*::*ABL1* halved after commencing imatinib, as well as the achievement of *BCR*::*ABL1* ratios of ≤10% IS were associated with molecular responses and event-free survival. The reduction ratio of *BCR*::*ABL1*, measured as the ratio of the 3 month *BCR*::*ABL1* divided by the pre-imatinib level, also predicted responses.

A *BCR*::*ABL1* ratio of ≤10% measured at 3 months of tyrosine kinase inhibitor (TKI) therapy, termed an early molecular response (EMR), has consistently been demonstrated to be an important prognostic indicator.[2-4] Nevertheless, the European LeukemiaNet (ELN) recommend intervention for treatment failure only if the ratio remains above 10% upon repeat analysis within 3 months.[5] The reason is that some patients with a ratio >10% at 3 months will have a reduction to within the optimal response category without treatment intervention by 6 months. Studies have determined that such patients can be identified by the initial rate of *BCR*::*ABL1* reduction measured at 3 months.[6,7] Accurate identification of the

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patients who should switch therapy to reduce the risk of disease progression and death is critical. A single molecular test is considered insufficient to take such an important decision as a change of treatment. Imatinib is in general safe and the side-effects are usually mild. The toxicity profile of second- and third-generation inhibitors is different to some degree. Several types of vascular events have been documented in patients treated with these more potent inhibitors and individual patient co-morbidities must be considered for treatment decisions.[8] Therefore, enhanced risk prediction of treatment failure is ideal.

The velocity of the initial response to TKI therapy can provide an early indication of whether a patient is responsive to targeted BCR::ABL1 inhibition. Velocity can be measured by the change in *BCR*::*ABL1* ratio from baseline to 3 months of TKI therapy. The baseline *BCR*::*ABL1* ratios are variable and provide no prognostic information.[6] For example, a patient with a *BCR*::*ABL1* ratio at baseline of 10%, which remains at 10% at 3 months has clearly not responded to TKI therapy, and treatment failure is indicated. Whereas, a patient with 100% *BCR*::*ABL1* at baseline who achieves a 1-log reduction of *BCR*::*ABL1* to 10% at 3 months, has had a substantial response and treatment intervention is not warranted. Ceran et al. measured the velocity of response as the ratio of the *BCR*::*ABL1* values from baseline to 3 months,[6] and defined this ratio as the 'reduction ratio'.[1] They determined that the optimal reduction ratio to predict a major molecular response was 0.04. However, the day of sample collection of the 3 month timepoint can vary from as early as 1.5 months after commencing TKI to as late as 4.5 months.[9] Therefore, the reduction ratio for a patient with a constant *BCR*::*ABL1* decline will change over time depending on the day of the 3 month collection. Perhaps a more accurate measure of the velocity of *BCR*::*ABL1* reduction is the *BCR*::*ABL1* halving time. This is the number of days over which *BCR*::*ABL1* halves on TKI therapy. Importantly, the halving time calculation takes into account the number of days between the baseline sample collection and the day of sample collection after commencing TKI therapy. The *BCR*::*ABL1* halving time should remain constant for patients with an exponential decline, irrespective of the time lapse between baseline and the 3 month collection timepoint.[7] Ceran et al. determined that the optimal *BCR*::*ABL1* halving time to predict a major molecular response was 24 days.

The study of 40 patients was a small cohort, however, it provides important confirmatory data for the relevance of the velocity of *BCR*::*ABL1* transcript decline. Furthermore, the rate of decline measured from baseline to 3 months was more important for the prediction of a deep molecular response than the single *BCR*::*ABL1* ratio measured at 3 months. Achieving a deep molecular response is a critical milestone molecular response for patients who aim to cease therapy in an attempt to achieve treatment-free remission. The study also contributed to the growing body of evidence that measuring *BCR*::*ABL1* transcript kinetics using a molecular method where *ABL1* is the control gene is possible.[10-13] It had been suggested that limitations related to the use of *ABL1* for real-time quantitative PCR analysis would preclude a reliable assessment of the kinetics of response since most methods that amplify *ABL1*, also amplify *BCR*::*ABL1*.[6]

In conclusion, measuring *BCR*::*ABL1* ratios at early timepoints after commencing TKI therapy remains an important prognostic indicator. Importantly, the rate of initial *BCR*::*ABL1* decline from the baseline measurement is a better predictor than a single measurement at 3 months for some patients.

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