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ddeeper Than Deep: Can ddPCR Predict Successful Imatinib Cessation?

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Summary

BCR-ABL1 transcripts at imatinib cessation were quantified by ddPCR for 175 patients on the STIM2 trial. Patients with *BCR-ABL1* transcripts below a defined cut-off had a twelve-month molecular recurrence rate of 46% versus 68% for those above the cut-off. Implications of using ddPCR in forecasting successful imatinib cessation are discussed.

In this issue of *Clinical Cancer Research*, Nicolini and colleagues provide an update on the open-label, phase II STop IMatinib 2 (STIM2) study evaluating the feasibility of stopping imatinib safely[1]. Trial eligibility was restricted to chronic phase CML (CP-CML) patients after at least two years of deep molecular response (DMR) on first-line imatinib, defined as no detectable *BCR-ABL1* transcript on a minimum of five data points with a sensitivity of >4.5 logs. The national study was coordinated across 29 centers in France and followed 218 patients. The 'per protocol' STIM2 cohort (199 of the 218 patients) excluded prior interferon-α exposure, prior tyrosine kinase inhibitors (TKIs) or <2 years of uninterrupted DMR. The team also evaluated the dataset for predictors of successful treatment-free remission (TFR), included digital droplet PCR (ddPCR).

This study reinforces two important points. First, we can anticipate a ~50% molecular recurrence rate for TKI cessation trials in properly selected CP-CML patients making a first attempt at TFR after first line imatinib therapy. On the STIM2 trial, 107/218 patients (49%) experienced molecular recurrence within the first year, defined as either loss of major molecular response at any time point or a 1-log rise in *BCR-ABL1* transcript levels across two consecutive time points. Second, molecular recurrences will occur within the first half-year, and the majority (103/107) within six months of imatinib cessation[1]. It is worth noting that the EURO-SKI trial, which included more heterogeneous patients, yet still a majority attempting TFR post imatinib, found a similar rate of successful TFR, but continued, low-level recurrence beyond 12 months, suggesting that late recurrence may be more common

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Disclosure of Potential Conflicts of Interest

MWD is a paid advisory board member or consultant at Blueprint Medicines, Pfizer, Takeda, Ascentage Pharma, Humana, Incyte, TRM, Sangoma, Fusion Pharma, Adelphi, and Novartis. He is on a study management committee at Blueprint Medicines and Takeda.

that suggested by the STIM2 study[2]. Identifying biomarkers to prospectively identify patients likely to maintain TFR is of considerable clinical importance.

Can we do better regarding to predict the success rate of imatinib cessation for a given cohort? One possibility is that, even among patients in DMR, numerical differences in depth of response hold predictive power. Once *BCR-ABL1* transcript levels reach the limit of detection with the current standard technology, RT-qPCR, which adheres to well-designed international protocols and mandates certified calibration standards, response depths fall into the category of "at or below Molecular Response 4.5 (MR4.5)" and cannot be ranked. Nicolini et al[1]. investigated the use of droplet digital PCR (ddPCR) as a *more-sensitive-than-RT-qPCR* (MR4.9 vs. MR4.7) technology to explore this question[1]. The findings, summarized below, are intriguing. The authors emphasize that incorporation of ddPCR into TKI cessation trial design is not yet ready for prime time and they are not advocating for it (yet) for two reasons. First, a major, coordinated protocol modification would be required to bring ddPCR into wide use for patient stratification. In particular, it would be challenging to standardize ddPCR readings expressed on the international scale (IS) across labs. The assay requires careful calibration in order to manage signal-to-noise issues. Second and importantly, strict enforcement of this criterion as a trial entry requirement would exclude some patients capable of going on to achieve a sustained TFR, pointing toward the need for additional predictive biomarkers that do not rely on *BCR-ABL1* transcript quantitation.

The authors used ddPCR to quantify *BCR-ABL1* transcript level for 175 patients with undetectable transcripts by RT-qPCR for at least two years prior to imatinib cessation. They found that the most appropriate way of analyzing the data was to break the patient populations into two categories (Figure 1): *(i)* individuals with undetectable transcripts by ddPCR using a detection threshold of 0.0013%^{IS} (100 patients) and individuals with a ddPCR-positive measurement below the median value of 0.0023%^{IS} (37 patients) versus *(ii)* individuals with a ddPCR-positive measurement at or above the median value of 0.0023%^{IS} (38 patients). A predictive signature was discernable from this treatment of the data. Briefly, group *(i)* exhibited a lower risk of molecular recurrence than group *(ii)* at twelve months (46% vs. 68%)[1].

Where does this leave us in terms of predictive power? There was a ~1.5-fold (at twelve months) higher probability of molecular recurrence in group *(ii)*. However, some individuals within this group successfully maintained TFR (32%), compared to 54% for the better-risk group (Figure 1). Inspection of the ddPCR *BCR-ABL1*^{IS} data (Figure 3C in [1]) reveals a substantial number of 'borderline' cases that are precariously close to the median value. It would be interesting to know whether the three cases furthest above the median experienced molecular recurrence.

Is this as good as it gets for STIM trial results, or could a hypothetical "STIM-dd" improve the percentage of successes? If "ddPCR <0.0023%" was added to the STIM2 entry criteria, we estimate the predicted outcome would be ~54% TFR at twelve months, instead of the 49% TFR at twelve months in the 175 ddPCR-analyzed patients on the STIM2 trial. This trial design would certainly exclude some individuals capable of maintaining TFR but not meeting this new inclusion criterion. The authors are clear in stating that this is not a trade

worth making. They do conclude their report by expressing their belief that ddPCR is a promising tool in discontinuation trials and by noting that discussions are underway on how best to incorporate and standardize this technology in a future algorithm of residual disease evaluation, probably in complement to RT-qPCR[1].

Bringing TFR to the 'real world' outside of clinical trials must consider practical issues such as frequency of molecular monitoring versus the level of inconvenience presented to patients. A recent model examining less intense, more feasible molecular monitoring schemes may offer one step toward making safe discontinuation a reality for more patients[3].

Is it important to know in advance who is most likely to maintain TFR? If we could offer patients considering a trial of TKI cessation a conveniently measured, robust predictive binary "yes/no" assessment, there would of course be interest. If one favors simply taking the empirical test, the suspense is not unbearable since molecular recurrence generally happens within 6 - 12 months. A more pressing need is to learn how to bring more patients into sustained TFR, particularly those who have had one unsuccessful attempt at TKI cessation. In STIM2, is there something that could have been done, or that could still be done, to bring the 107 patients who had molecular recurrence into the TFR fold (e.g. longer on TKI, switch to a more potent TKI, and/or wait for a hint in the form of a lower, 'odds-stacking' ddPCR reading)? The authors did not find an association between duration of treatment or duration of DMR and ddPCR value, suggesting that lowering the ddPCR value in STIM2-qualified candidates by extending treatment duration is not straightforward. Given the clinical implications of this observation, validation in an independent cohort would be important. One approach to a successful TFR on the second attempt, featured in trials such as RE-STIM, is to simply try again once a durable DMR has been re-gained. One-third of eligible patients remained in TFR after a second discontinuation attempt[4]. The big challenge is that at a biological level, our understanding of the divide between successful TFR versus molecular recurrence remains rudimentary, though intriguing hints have been reported[5-7]. Well-designed, biomarker-heavy studies such as STIM2 will be critical for elucidating the mechanisms of sustained TFR and for discovering biomarkers that predict the success or failure of TFR.

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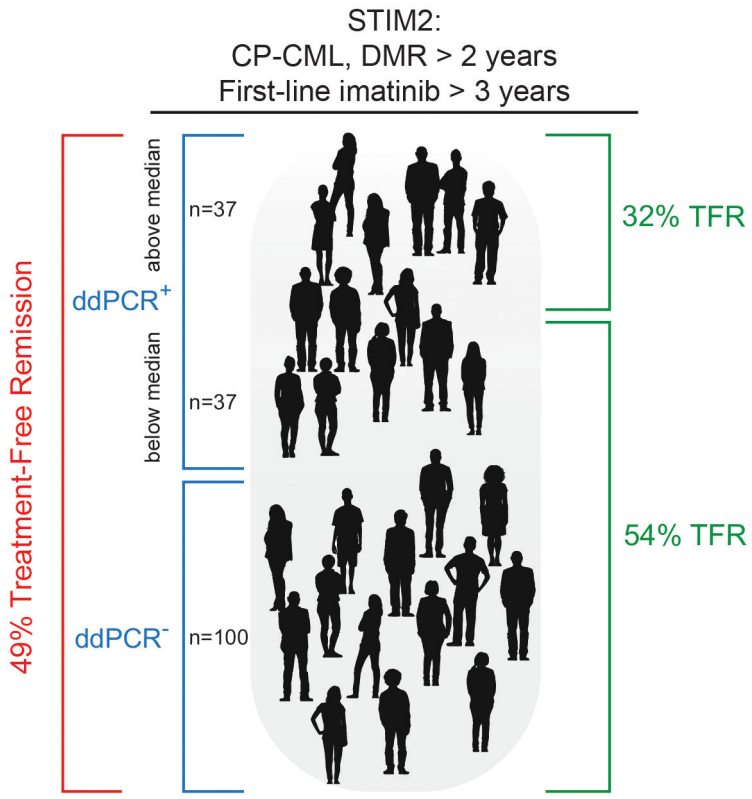

Figure 1.

Droplet digital polymerase chain reaction (ddPCR) analysis at the time of imatinib cessation stratifies STIM2 participants according to probability of successful treatment-free remission (TFR). Among 175 patients for whom *BCR-ABL1* ddPCR data was collected and expressed on the international scale, 100 patients were ddPCR-negative and 75 patients were ddPCR-positive. For TFR probability analysis, the 37 ddPCR-positive patients below the median value were grouped with the ddPCR-negative patients. The other group was comprised of the 37 ddPCR-positive patients above the median value. The TFR values shown are for the two groups at twelve months post-imatinib cessation.