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Molecular dynamics during reduction of TKI dose reliably identify molecular recurrence after treatment cessation in CML

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Abstract:

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Molecular dynamics during reduction of TKI dose reliably identify molecular recurrence after treatment cessation in CML

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Running title: Dynamics of TKI reduction identify CML recurrence

Continuous treatment with tyrosine kinase inhibitors (TKI) induces a fast initial response and leads to long-term remission in most patients with chronic myeloid leukaemia (CML) [1]. Consequently, the annual mortality in CML has decreased to 1–2% [2] and patients with CML approach the life expectancy of the general population [3]. However, continuous treatment with TKI is costly and associated with significant side effects. Therefore, alternative treatment strategies are needed. Although TKI dose reductions during established molecular remission have only been considered recently [4,5], the potential of TKI treatment cessation for CML patients in sustained molecular remission has been studied in greater detail [6,7]. Several studies consistently report that about 50% of CML patients remain in treatment-free remission (TFR) for many years while most of the other patients present with recurring disease levels after stopping TKI [8,9]. Although TKI treatment duration and time in molecular remission are associated with higher TFR rates [9], a reliable prospective prediction of disease recurrence for individual patients is not possible yet. The DESTINY trial (NCT01804985) differs from other TKI stop studies in that TKI treatment is reduced to 50% of the standard dose for 12 months prior to cessation, including 125 patients in stable MR4 (BCR-ABL1^{IS} <0.01%) and 49 patients in stable MR3 (BCR-ABL1^{IS} <0.1%) but not MR4 before entry. The trial demonstrates that this strategy improves the fraction of MR4 patients in successful TFR to above 70% at 2 years after treatment cessation while also about 36% of MR3 patients retained TFR [10,11]. Here, we evaluate the BCR-ABL1^{IS} values monitored during dose reduction and suggest that they can serve as a predictor of individual CML recurrence after TKI cessation independent of the BCR-ABL1^{IS} values at study entry.

BCR-ABL1^{IS} levels are regularly obtained from peripheral blood cells of CML patients to monitor their leukaemia load. Within DESTINY, BCR-ABL1^{IS} was available for all 174 patients measured prior to dose reduction (time point 0), monthly during the 12 months dose reduction period and monthly or every second month thereafter until month 36. Molecular recurrence was defined as the first of two consecutive BCR-ABL1^{IS} measurements >0.1% or using particular *case reports* indicating recurrences without achieving BCR-ABL1^{IS} >0.1%. In total, 67 recurrences were observed of which 12 occurred during the dose reduction period. At recurrence, TKI treatment at full dose was reinitiated. In order to quantify the change of BCR-ABL1^{IS} during the 12 months dose reduction period, we applied a linear regression to each patient and estimated the individual slope measured on the log[BCR-ABL1^{IS}] scale (Figure 1A), if at least 3 non-zero BCR-ABL1^{IS} values were available. Thereby we excluded 3 of 174 patients. The correlation of individual slopes and molecular recurrence was quantified by logistic regression analysis.

We observed that the majority of patients had either negative slopes (i.e. BCR-ABL1^{IS} decreasing) or low positive slopes close to zero (Figure 1B), indicating that their BCR-ABL1^{IS} levels did not rise substantially, if at all, during the dose reduction period. In contrast, there is a group of patients with considerably higher slopes, indicating an increase in BCR-ABL1^{IS}. Logistic regression analysis shows that for an additional 0.01 log[BCR-ABL1^{IS}] increase per month in the slope parameter, there was a 28% increased chance of recurrence (Odds Ratio (OR): 1.28; 95% CI: 1.17-1.42) at any time (Figure 1C). This also applies if the MR3 and MR4 subgroups are analysed separately (Supplemental Figure 1) and indicates that an increase of BCR-ABL1^{IS} during the dose reduction period is strongly associated with eventual molecular recurrence.

We identified the 95%-quantile of a normal distribution fitted to the negative/low BCR-ABL1^{IS} slopes at 0.068 log[BCR-ABL1^{IS}] increase per month as a suitable cut off to split the patient cohort into 80.7% with negative/low slopes and 19.3% with high slopes (Figure 1B, Supplemental Material). Irrespective of the response level prior to dose reduction, 72.5% of the patients presenting with a negative/low slope during dose reduction remained recurrence-free at 2 years after stopping treatment. In the high slope group, 87.9% of the patients had disease recurrence, while only 4 patients (12.1%) did not report the adverse event, of which 3 were censored. The OR calculated for the categorized patients is 19.1

(95% CI: 6.3-57.9, Figure 1D) indicating that the risk of recurrence is dramatically increased for the high slope group compared to the group with negative/low slopes.

Almost all TFR studies hitherto have focussed on patients in stable MR4 while the DESTINY trial also included 49 MR3 patients. Having a closer look at their response during dose reduction separately, it appears that 30.6% of the MR3 patients presented with high slopes, while only 14.8% of the patients in MR4 showed similarly elevated slopes. I.e., patients in MR3 have a 2.6-fold higher chance to present with highly increasing BCR-ABL1^{IS} levels during dose reduction compared to patients in MR4 (OR: 2.6, 95% CI:1.2-5.6).

Although less common than with high slopes, recurrences after stopping TKI nevertheless occurred in patients with negative/low slopes during the dose reduction period in both the MR3 and MR4 cohorts. A detailed analysis of the distribution of the individual slopes of those patients (Figure 2A) reveals that there is a tendency for lower slopes in the remission cohort as compared to the recurrence cohort, thereby underpinning our findings of the overall logistic regression model.

Our findings suggest an amended strategy for TKI cessation studies, exploiting additional information from intermediate dose reduction: After the 12 months dose reduction period, patients should only be stopped if they are still below MR3 (i.e. no early recurrence) and additionally show a negative/low BCR-ABL1^{IS} slope during this period. Patients with high slopes should return to full dose TKI treatment, as a future recurrence is extremely likely and they do not even sufficiently manage the half dose reduction. Enforcing such a strategy within the DESTINY protocol could have further increased the fraction of recurrence-free patients among those patients that stopped TKI after the 12 months dose reduction (Figure 2B). For completeness we note that patients with continuing negative BCR-ABL1^{IS} measurements are rare within DESTINY but might occur more often in other cessation studies with more stringent entry criteria. While we exclude such patients (n=3) from our analysis, this cohort might have to be considered separately in future studies. However, as long as no measurable increase of BCR-ABL1^{IS} levels can be detected, those patients are not considered as high risk anyway.

From our analysis we conclude that the individual molecular dynamic during TKI dose reduction is a promising predictor for a molecular recurrence after TKI cessation. In particular, the exclusion of patients with highly increasing BCR-ABL1^{IS} slopes during the dose reduction period from complete TKI cessation is likely to reduce the overall number of recurrences, and to increase the TFR success rate on stopping TKI. For the clinical decision about whether to stop TKI treatment after the dose reduction period, we have estimated the positive predictive value (i.e. probability of losing TFR for patients with high slope) and the negative predictive value (i.e. probability of keeping TFR for patients with negative/low slope) to be 81.0% and 72.5%, respectively, based on the 159 DESTINY patients at risk at month 12 and a recurrence prevalence of 34.6%. Conceptually, our results demonstrate that frequent monitoring of molecular response during dose reduction can inform patient management by minimising the risk for CML recurrence on a subsequent TFR attempt. A validation of our quantitative estimates using an independent cohort is necessary to confirm our predictions and to compare or complement our approach with further biomarkers of TFR.

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Data sharing: Data of the DESTINY trial are already presented in references number 10 and 11.

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Figure Legends

Figure 1: BCR-ABL1^{IS} level monitored during dose reduction are predictive for individual CML recurrence after TKI cessation.
(A) BCR-ABL1^{IS} dynamics of two patients upon dose reduction. The left example corresponds to a patient with a low positive slope of the BCR-ABL1^{IS} values during dose reduction period (green line indicates the slope) that remains in TFR after therapy stop. The right example illustrates a patient who is characterized by a high slope during the 12 months dose reduction period (red line) and presents with a recurrence after TKI stop (red dots).
(B) Histogram for patient-specific estimates of the individual BCR-ABL1^{IS} slope during the 12 months dose reduction period (n=171). The 95%-quantile (red dashed line) of the normal distribution fitted to patients with negative/low slope (green curve) is taken as a cut-off parameter (at 0.068 log[BCR-ABL1^{IS}] per month) to separate patients with high slopes (red curve).
(C) Logistic regression curve for patient-specific estimates of the individual BCR-ABL1^{IS} slope during the 12 months dose reduction period (n=171) with corresponding odds ratio (OR) and 95% confidence interval (CI) per 0.01 log-increase per month. Patients are separated into cohorts with negative/low slopes (green area) and patients with high slopes (red area) by applying the cut-off parameter announced in (B).
(D) Fraction of patients with and without recurrence in the cohorts with negative/low and high slopes during dose reduction (n=171) and corresponding odds ratio (OR) with 95% confidence interval (CI).

Figure 2: Subgroup and recurrence-free survival analysis.
(A) Subgroup analysis of the patients with negative/low slope (n=138): The central part reproduces an inset of the logistic regression curve for patient-specific estimates of the individual BCR-ABL1^{IS} slope during the 12 months dose reduction period. Patients are categorized according to their prior BCR-ABL1^{IS} level as either MR3 (rhombi) or MR4 (filled circles). The upper and lower panel depict the slope distributions of patients with and without molecular recurrence, respectively, stratified for the molecular response level before dose reduction (i.e. MR3: dark shaded, MR4: light shaded). Small ticks indicate the estimates of the individual BCR-ABL1^{IS} slopes and black bars illustrate the mean of the slope of the respective group (upper panel: mean of MR3 recurrence group = 0.017 and MR4 recurrence group = 0.014; lower panel: mean of MR3 non-recurrence group = -0.005 and MR4 non-recurrence group = 0.006).
(B) Recurrence-free survival of patients with either negative/low (green) or high slope (red) during the 12 months reduction period (n=171). The patients with high slopes are further separated as to whether they present with disease recurrence during the half dose period (light red) or after treatment stop.