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Review Article

BCR-ABL1 Transcript Kinetics and Treatment-Free Remission in Patients with Chronic Myeloid Leukemia

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Summary

Early BCR-ABL1 kinetics predict which patients will reach a deep molecular response, and reaching one is the entry requirement for attempting to stop treatment. It does not follow that kinetics predict who will stay in remission after stopping, and the largest comparison found that they do not.

Objectives: To review the published evidence on BCR-ABL1 transcript kinetics and treatment-free remission in chronic myeloid leukaemia: what proportion of patients maintain remission after stopping, when relapse occurs, which variables predict it, and whether early kinetic measures add anything to the prediction.

Material and Methods: Narrative review of discontinuation trials, real-world cohorts, modelling studies and consensus recommendations indexed in PubMed and the major haematology journals. Studies were eligible if they reported treatment-free remission outcomes after tyrosine kinase inhibitor discontinuation in a defined chronic myeloid leukaemia population, or the predictive performance of molecular response measures. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In the largest discontinuation trial, 434 of 728 patients (61 per cent, 95% CI 57-64) remained in major molecular response at 6 months and 309 of 678 (46 per cent, 42-49) at 36 months. Duration of tyrosine kinase inhibitor treatment and of deep molecular response before stopping were confirmed as predictors of loss at 6 months, with transcript type added as a third. In the earliest trial, molecular relapse occurred in 61 of 100 patients and 80 per cent of those relapses fell within the first 6 months. Where deep response had been sustained for only one year and total treatment was under three years, relapse-free survival was 16.7 per cent at 12 months and the trial was terminated early. Comparing early measures in 408 real-world patients, halving time and residual disease at month 3 performed similarly and residual disease at month 6 performed best for predicting deep response, with areas under the curve of 0.81 to 0.92, but the initial molecular response did not predict treatment-free remission maintenance.

Conclusion: Early kinetics identify who will achieve a deep response and are useful for that purpose. What predicts staying in remission after stopping is duration, of treatment and of deep response, rather than how quickly the transcript fell in the first months.

Abbreviations: CML – Chronic Myeloid Leukaemia, CML-CP – Chronic Phase CML, TKI – Tyrosine Kinase Inhibitor, TFR – Treatment-Free Remission, MMR – Major Molecular Response, DMR – Deep Molecular Response, MR4 – BCR-ABL1 IS ≤0.01 Per Cent, MR4.5 – BCR-ABL1 IS ≤0.0032 Per Cent, IS – International Scale, HT – Halving Time, ELTS – EUTOS Long-Term Survival Score, KDM – Kinase Domain Mutation.

Keywords: Chronic Myeloid Leukaemia; BCR-ABL1; Treatment-Free Remission; Halving Time; Deep Molecular Response

Introduction

Chronic myeloid leukaemia was transformed by tyrosine kinase inhibition, and life expectancy for patients responding well now approaches that of the general population [1,2]. That success created a question the disease did not previously pose: whether treatment can ever be stopped, in people who may otherwise take a daily drug for forty years [3].

Discontinuation is possible because response is measurable with unusual precision. The BCR-ABL1 transcript is quantified against a reference gene and expressed on an international scale, so depth of response can be reported to four or more logs below the standardised

baseline [4,5]. Deep molecular response at MR4 or MR4.5 became the entry criterion for stopping attempts [6,7].

Alongside this, early transcript kinetics were shown to predict which patients would reach those depths. The transcript level at three or six months, and more recently the time taken for the transcript to halve, both carry prognostic weight for subsequent response [8,9,10]. It has been natural to assume the same measures would predict who could stop successfully.

This review sets out what discontinuation actually achieves, when relapse occurs, which variables predict it, and whether the early kinetic measures transfer from predicting depth to predicting durability.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of treatment discontinuation in chronic myeloid leukaemia. Search terms combined chronic myeloid leukaemia with treatment-free remission, tyrosine kinase inhibitor discontinuation, deep molecular response, BCR-ABL1 halving time, transcript kinetics and molecular relapse. Reference lists of retrieved trials and recommendations were screened by hand.

Eligibility: Studies were included if they reported outcomes after tyrosine kinase inhibitor discontinuation in a defined chronic myeloid leukaemia population, or evaluated the predictive performance of molecular response measures for deep response or for treatment-free remission. Modelling studies are cited where they address prediction directly and are identified as such.

Data extraction and handling: Design, cohort size, entry criteria, definition of molecular relapse, follow-up duration and reported outcome estimates were extracted as published. Entry criteria are stated alongside every remission figure, because trials differ in required treatment duration, required depth and duration of deep response, and those differences drive most of the variation between reported success rates. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What stopping achieves: The largest discontinuation trial enrolled patients treated with any tyrosine kinase inhibitor for at least three years who had sustained MR4 for at least one year. Among 728 evaluable patients, 434 (61 per cent, 95% CI 57 to 64) remained in major molecular response at 6 months, and 309 of 678 (46 per cent, 95% CI 42 to 49) at 36 months (Figure 1) [11,12].

The earlier trial that established feasibility enrolled 100 chronic-phase patients with undetectable transcripts sustained for at

least two years on imatinib. Molecular relapse occurred in 61 patients, and treatment-free survival was 39 per cent at five years with median follow-up of 77 months [13,14]. A parallel study using similar criteria reported treatment-free remission of 47.1 per cent at 24 months among 40 patients [15].

Roughly half of carefully selected patients therefore stay off treatment long term, and the figure has been consistent across trials and drugs [11,13,16]. Restarting after molecular relapse restores response in almost all cases, which is what makes the attempt reasonable [6,13].

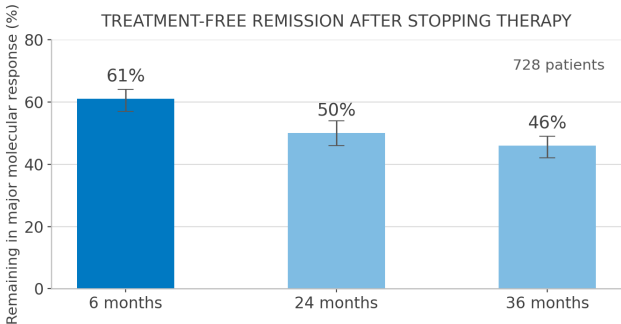


Figure 1: Proportion remaining in major molecular response after discontinuation in 728 patients [11,12]

Relapse is an early event: The timing is consistent and clinically important. In the earliest trial, 80 per cent of the 61 molecular relapses occurred within the first six months after stopping (Figure 2) [14], and in the largest trial loss of major molecular response occurred primarily within the same window [11,12]. Longer follow-up of the first cohort found no additional relapses beyond a median of 65 months [13].

That distribution dictates monitoring intensity. Transcript measurement is required monthly during the first six months, and the risk after two years of sustained remission is low enough that intervals can be extended [6,7]. Late losses do occur, and the factors predicting them differ from those predicting early loss, which is discussed below [12].

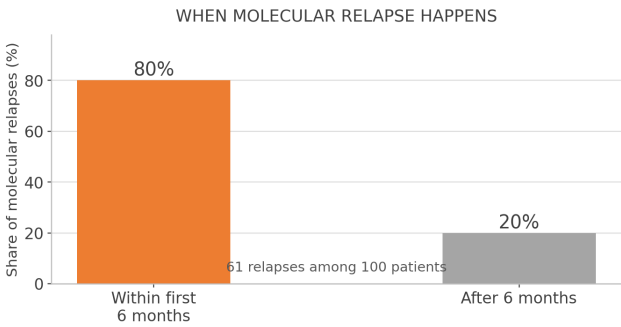


Figure 2: Timing of molecular relapse after imatinib discontinuation [13,14]

Study	n	Entry criteria	Principal reported finding
STIM1 [13,14]	100	Undetectable ≥2 years	39% treatment-free at five years
TWISTER [15]	40	Undetectable ≥2 years	47.1% at 24 months
EURO-SKI [11,12]	728	MR4 ≥1 year, TKI ≥3 years	61% at 6 months, 46% at 36 months
STIM2 [17]	—	First-line imatinib	Kinetics of early and late recurrence described
D-FREE [18]	21	MR4.5 ≥1 year, TKI <3 years	16.7% at 12 months; terminated early
Real-world cohort [19]	408	Observational	Early response predicts depth, not maintenance

Table 1: Principal discontinuation studies, with entry criteria and the finding as reported by the original investigators

Duration is what predicts success: The final analysis of the largest trial confirmed duration of tyrosine kinase inhibitor treatment and duration of deep molecular response before stopping as significant predictors of losing major molecular response at six months, and added transcript type as a third factor, with e13a2 carrying worse prospects than e14a2 [12,20,21]. For losses occurring after six months, the significant factors were treatment duration, percentage of blasts in peripheral blood and platelet count at diagnosis [12].

The clearest demonstration is a trial that violated the duration requirement deliberately. Twenty-one patients who had maintained MR4.5 for one year discontinued dasatinib after less than three years of total treatment. Seventeen relapsed, giving estimated relapse-free survival of 16.7 per cent at 12 months, and the study was terminated early under its own safety monitoring rules (Figure 3) [18].

Setting that against 61 per cent at six months in the larger trial, where treatment had lasted at least three years, isolates duration as the operative variable [11,18]. Depth of response was if anything greater in the terminated study, since MR4.5 is deeper than the MR4 required in the larger one.

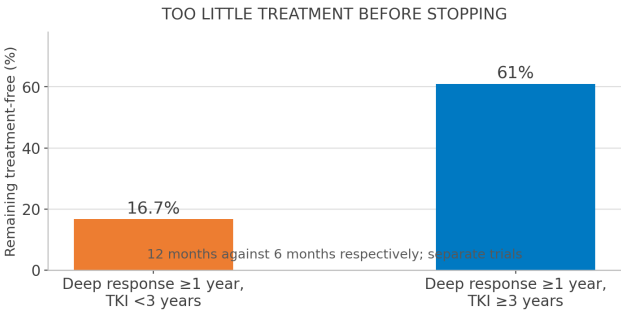


Figure 3: Outcome when total treatment duration falls below three years, against the larger trial [11,18]

What early kinetics do and do not predict: Transcript halving time has been proposed as an early predictor, and it performs well for the endpoint it was developed against. Shorter halving time predicts achievement of molecular response in newly diagnosed patients [9], and early kinetics predict subsequent achievement of the deep response that makes a stopping attempt possible [10].

A real-world cohort of 408 patients compared the available early measures directly, testing a prognostic score, halving time, and residual disease at months 3 and 6 against three endpoints. Halving time and residual disease at month 3 performed similarly. Residual disease at month 6 performed best for predicting optimal response, with areas under the curve between 0.81 and 0.92 and cut-offs of 0.11 per cent for MR4 at month 24 and 0.12 per cent for MR4.5 at month 48 (Figure 4) [19].

The negative finding is the one that matters here. The same analysis found that initial molecular response predicted deep molecular response but not treatment-free remission maintenance [19]. Early kinetics identify who will reach the door; they do not identify who will stay outside it once through.

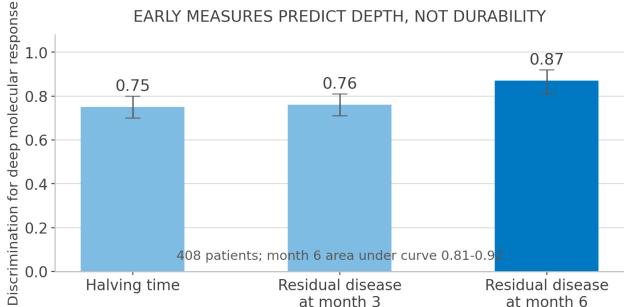


Figure 4: Discrimination of early measures for deep molecular response in 408 patients [19]

Variable	Predicts deep response?	Predicts treatment-free remission?
Transcript halving time	Yes	Not demonstrated [9,10,19]
Residual disease at month 3	Yes	Not demonstrated [8,19]
Residual disease at month 6	Best performer	Not demonstrated [19]
Duration of TKI treatment	Not applicable	Yes, early and late loss [11,12,18]
Duration of deep response	Not applicable	Yes, early loss [11,12]
Transcript type e13a2 vs e14a2	—	Yes, e13a2 worse [12,20,21]

Table 2: Which measures predict which endpoint

Discussion

The finding at the centre of this review is a negative one, and negative findings about biomarkers are easy to overlook. Halving time and early residual disease are good predictors of deep molecular response [8,9,10], deep molecular response is the entry criterion for stopping [6,7], and it is a short step to assuming that early kinetics therefore predict successful stopping. The direct comparison shows they do not [19].

What does predict success is duration: of treatment before stopping, and of deep response before stopping [11,12]. The trial that stopped dasatinib after less than three years despite MR4.5 sustained for a year makes the point unusually cleanly, with relapse-free survival of 16.7 per cent against 61 per cent where the duration requirement was met [11,18].

Why depth and durability come apart

A plausible account is that transcript level measures the differentiated leukaemic compartment while relapse originates in a quiescent stem cell population that the assay does not see [22,23]. Kinetics of transcript decline describe how efficiently the drug clears cells that are dividing; they say nothing about how many quiescent cells remain.

Duration of exposure, by contrast, plausibly does affect that reservoir, through attrition over years rather than through rapid killing. If so, duration and kinetics are measuring different compartments, and the observation that only duration predicts durability is what the biology would lead one to expect rather than an anomaly [22,23].

Study limitations

The limitations belong to the underlying literature. Discontinuation trials differ in required treatment duration, required depth, required duration of deep response and definition of molecular relapse, so their success rates are not directly comparable [11,13,15,18]. Most enrolled patients treated predominantly with imatinib, and whether findings transfer to second-generation inhibitors used first line is incompletely established [11,16]. Assay standardisation on the international scale is good but not perfect, and the deepest response categories approach the limit of quantification, where reproducibility falls [4,5]. The comparison of early predictive measures is from a single real-world cohort [19]. And patients with prior resistance or kinase domain mutations are generally excluded from stopping attempts, so outcomes in that group rest on small series [24].

Two gaps deserve naming. No trial has randomised the duration of deep molecular response required before stopping, so the current thresholds rest on observational association rather than comparison [11,12]. And no study reviewed here identifies a measure that predicts treatment-free remission independently of duration, which is what would allow patients to stop earlier than current criteria permit [19,25].

Conclusion

Roughly half of carefully selected patients with chronic myeloid leukaemia remain in remission after stopping tyrosine kinase inhibitor therapy, with 61 per cent still in major molecular response at six months and 46 per cent at three years in the largest trial. Relapse is an early event, with 80 per cent of losses occurring within six months, which is why monthly monitoring is required over that period. The variables that predict success are duration of treatment and duration of deep molecular response before stopping, together with transcript type; stopping after less than three years of treatment gave relapse-free survival of 16.7 per cent even where MR4.5 had been sustained. Early transcript kinetics, including halving time, predict achievement of deep molecular response well and do not predict maintenance of treatment-free remission, a distinction that the shared vocabulary of molecular response tends to obscure.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. Bower, H., Björkholm, M., Dickman, PW., Höglund, M., Lambert, PC., Andersson, TML. (2016) Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*, 34(24): 2851-2857.
2. Hochhaus, A., Larson, RA., Guilhot, F., Radich, JP., Branford, S., Hughes, TP., et al. (2017) Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*, 376(10): 917-927.
3. Mahon, FX. (2017) Treatment-free remission in CML: who, how, and why? *Hematology Am Soc Hematol Educ Program*, 2017(1): 102-109.
4. Cross, NCP., White, HE., Müller, MC., Saglio, G., Hochhaus, A. (2012) Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*, 26(10): 2172-2175.

5. Cross, NCP., White, HE., Colomer, D., Ehrencrona, H., Foroni, L., Gottardi, E., et al. (2015) Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia*, 29(5): 999-1003.
6. Hochhaus, A., Baccarani, M., Silver, RT., Schiffer, C., Apperley, JF., Cervantes, F., et al. (2020) European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*, 34(4): 966-984.
7. Saussele, S., Richter, J., Hochhaus, A., Mahon, FX. (2016) The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*, 30(8): 1638-1647.
8. Marin, D., Ibrahim, AR., Lucas, C., Gerrard, G., Wang, L., Szydlo, RM., et al. (2012) Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol*, 30(3): 232-238.
9. Iriyama, N., Fujisawa, S., Yoshida, C., Wakita, H., Chiba, S., Okamoto, S., et al. (2015) Shorter halving time of BCR-ABL1 transcripts is a novel predictor for achievement of molecular responses in newly diagnosed chronic-phase chronic myeloid leukemia treated with dasatinib: results of the D-first study of Kanto CML study group. *Am J Hematol*, 90(4): 282-287.
10. Shanmuganathan, N., Pagani, IS., Ross, DM., Park, S., Yong, ASM., Braley, JA., et al. (2021) Early BCR-ABL1 kinetics are predictive of subsequent achievement of treatment-free remission in chronic myeloid leukemia. *Blood*, 137(9): 1196-1207.
11. Saussele, S., Richter, J., Guilhot, J., Gruber, FX., Hjorth-Hansen, H., Almeida, A., et al. (2018) Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*, 19(6): 747-757.
12. Mahon, FX., Pfirrmann, M., Dulucq, S., Hochhaus, A., Guilhot, F., Richter, J., et al. (2024) European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in chronic myeloid leukemia: final analysis and novel prognostic factors for treatment-free remission. *J Clin Oncol*, 42(15): 1875-1880.
13. Etienne, G., Guilhot, J., Rea, D., Rigal-Huguet, F., Nicolini, F., Charbonnier, A., et al. (2017) Long-term follow-up of the French Stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. *J Clin Oncol*, 35(3): 298-305.
14. Mahon, FX., Réa, D., Guilhot, J., Guilhot, F., Huguet, F., Nicolini, F., et al. (2010) Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*, 11(11): 1029-1035.
15. Ross, DM., Branford, S., Seymour, JF., Schwarzer, AP., Arthur, C., Yeung, DT., et al. (2013) Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*, 122(4): 515-522.
16. Hochhaus, A., Masszi, T., Giles, FJ., Radich, JP., Ross, DM., Gomez Casares, MT., et al. (2017) Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*, 31(7): 1525-1531.
17. Dulucq, S., Nicolini, FE., Rea, D., Cony-Makhoul, P., Charbonnier, A., Escoffre-Barbe, M., et al. (2022) Kinetics of early and late molecular recurrences after first-line imatinib cessation in chronic myeloid leukemia: updated results from the STIM2 trial. *Haematologica*, 107(12): 2859-2869.
18. Kimura, S., Imagawa, J., Murai, K., Fujisawa, S., Tanaka, H., Fujioka, I., et al. (2023) Importance of TKI treatment duration in treatment-free remission of chronic myeloid leukemia: results of the D-FREE study. *Int J Hematol*, 117(6): 866-875.
19. Rousselot, P., Nicolini, FE., Cayuela, JM., Dulucq, S., Etienne, G., Rea, D., et al. (2024) The initial molecular response predicts the deep molecular response but not treatment-free remission maintenance in a real-world chronic myeloid leukemia cohort. *Haematologica*, 109(9): 2900-2909.
20. D'Adda, M., Farina, M., Schieppati, F., Borlenghi, E., Bottelli, C., Cerqui, E., et al. (2019) The e13a2 BCR-ABL transcript negatively affects sustained deep molecular response and the achievement of treatment-free remission in patients with chronic myeloid leukemia who receive tyrosine kinase inhibitors. *Cancer*, 125(10): 1674-1682.
21. Baccarani, M., Castagnetti, F., Gugliotta, G., Rosti, G., Soverini, S., Albeer, A., et al. (2019) The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia: an international overview. *Leukemia*, 33(5): 1173-1183.
22. Bhatia, R., Holtz, M., Niu, N., Gray, R., Snyder, DS., Sawyers, CL., et al. (2003) Persistence of malignant hematopoietic progenitors in chronic myelogenous leukemia patients in complete cytogenetic remission following imatinib mesylate treatment. *Blood*, 101(12): 4701-4707.
23. Chomel, JC., Bonnet, ML., Sorel, N., Bertrand, A., Meunier, MC., Fichelson, S., et al. (2011) Leukemic stem cell persistence in chronic myeloid leukemia patients with sustained undetectable molecular residual disease. *Blood*, 118(13): 3657-3660.
24. Branford, S., Yeung, DT., Ross, DM., Prime, JA., Field, CR., Altamura, HK., et al. (2013) Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML. *Blood*, 121(19): 3818-3824.
25. Radich, JP., Deininger, M., Abboud, CN., Altman, JK., Berman, E., Bhatia, R., et al. (2018) Chronic myeloid leukemia, version 1.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*, 16(9): 1108-1135.