

# Unplanned discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia

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**Abstract.** This study was conducted to investigate the outcomes of patients with chronic myeloid leukemia (CML) who discontinued tyrosine kinase inhibitor (TKI) treatment. A single-center retrospective analysis was performed, including 46 chronic-phase (CP) CML patients who achieved complete molecular response (CMR) with TKIs. TKI treatment was discontinued in 13 patients based on their requests. The BCR-ABL transcript levels were monitored in the peripheral blood by quantitative polymerase chain reaction analysis following treatment discontinuation. Of the 13 patients who discontinued TKI treatment, 7 remained in CMR, with a median follow-up of 26 months (range, 10-60 months). The remaining 6 patients lost CMR following TKI discontinuation; 2 of these patients achieved a second CMR following re-administration of TKIs, 2 patients spontaneously achieved CMR and 2 remained in complete hematological response (CHR) without TKI treatment with a median follow-up of 29.5 months (range, 10-52 months). In conclusion, the survival of patients who lost CMR following TKI discontinuation may not be affected, even without re-administration of TKIs. Vigilant observation is recommended for such patients. The limitations of this study included the small patient sample, retrospective design and patient heterogeneity. Therefore, the results must be interpreted with caution.

## Introduction

The emergence of tyrosine kinase inhibitors (TKIs) has significantly changed chronic myeloid leukemia (CML) treatment (1-3). With imatinib, ~40% of chronic-phase (CP) CML patients achieve a complete molecular response

(CMR) within 5 years, as determined by the sensitive reverse transcription quantitative polymerase chain reaction (qPCR) analysis (4,5). The estimated overall survival (OS) rate of CML patients treated with imatinib was reported to be 89 and 85% at 5 and 8 years, respectively (6). Next-generation TKIs have also been found to be effective for CML (7,8). Although CML patients primarily require lifelong treatment with TKIs, recent clinical studies demonstrated that approximately half of the patients in CMR who discontinued TKIs remained in CMR, whereas the remaining patients lost CMR (9-11).

The high cost of TKIs may be prohibitive for their administration (12). A significant proportion of patients have decided to discontinue TKI treatment, but their outcomes have not been reported. The aim of this study was to investigate the natural course of patients who voluntarily discontinue TKI treatment.

## Patients and methods

**Patients.** The medical records from the Hakodate Municipal Hospital were reviewed to identify all Philadelphia chromosome-positive CP-CML patients aged >18 years who achieved CMR with TKIs, such as imatinib, nilotinib and dasatinib, between August, 2002 and March, 2013. Certain patients had a history of prior treatment with interferon, hydroxycarbamide or busulfan. Our study protocol was approved by the Hakodate Municipal Hospital Institutional Review Board. Based on the Declaration of Helsinki, written informed consent was obtained from all participating patients.

**Treatment.** The patients were treated according to the European LeukemiaNet recommendations (13). We monitored the BCR-ABL transcript levels in the peripheral blood based on the recommendations of the Europe Against Cancer Program (14). CMR was defined as no detection of BCR-ABL/ABL transcript. The limit of detection with this method was  $<2 \times 10^5$  copy/ $\mu$ gRI. A complete hematological response (CHR) was defined as a white blood cell count of  $<1.0 \times 10^4/l$ , a platelet count of  $<45 \times 10^4/l$ , a proportion of basophils  $<5\%$ , with no blast cells in the peripheral blood and no splenomegaly. qPCR analysis of the peripheral blood was performed once a month for 2 years after the initiation of TKI therapy and once every 3 months thereafter. Following TKI discontinuation, qPCR analysis was performed once a month.

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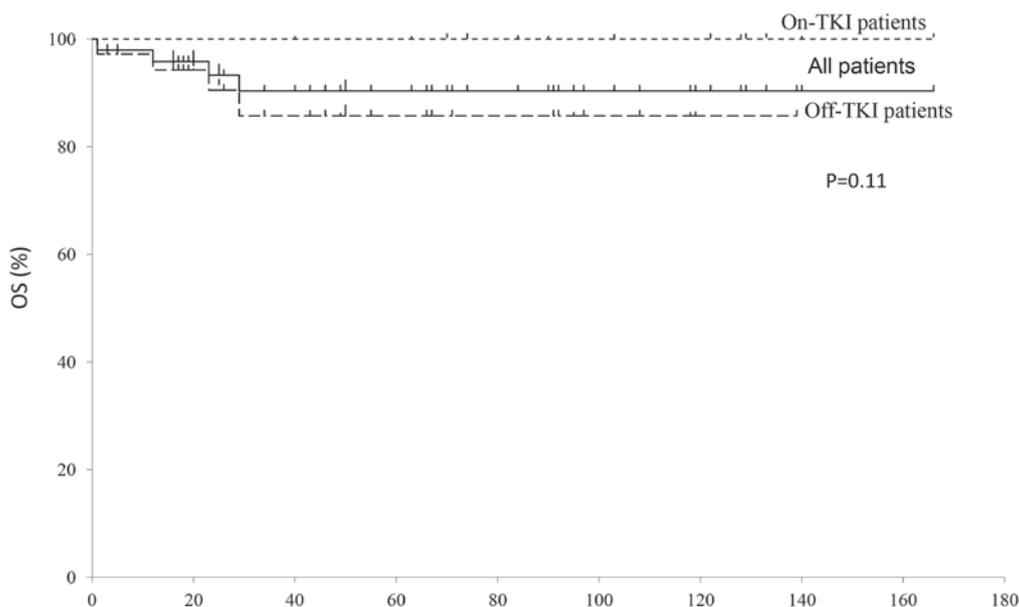


Figure 1. OS from initiation of TKI treatment in all patients, those who continued TKI treatment (on-TKI) and those who discontinued treatment (off-TKI). The 8-year OS rate of all the patients was 83%. OS, overall survival; TKI, tyrosine kinase inhibitor.

Table I. Patient characteristics.

Characteristics	On TKIs (n=33)	Off TKIs (n=13)	P-value
Median age, years (range)	64 (34-84)	56 (39-85)	0.6661 <sup>a</sup>
Gender (male/female)	24/9	10/3	0.999 <sup>b</sup>
First-line TKI			0.0226 <sup>c</sup>
Imatinib	25	13	
Dasatinib	6	0	
Nilotinib	6	0	

<sup>a</sup>Median test. Fisher's exact test. <sup>b</sup>G-test. TKI, tyrosine kinase inhibitor.

Table II. Characteristics of patients who discontinued TKI treatment.

Characteristics	No.
Duration of TKI therapy, months Median (range)	74 (27-158)
Reasons for TKI discontinuation	
Surgery for accidents	1
Surgery for malignancy	4
High cost	8

TKI, tyrosine kinase inhibitor.

**Analysis.** The OS was defined as the time from the initiation of TKI treatment until death from any cause or the date of the last follow-up. In patients who discontinued TKI treatment,

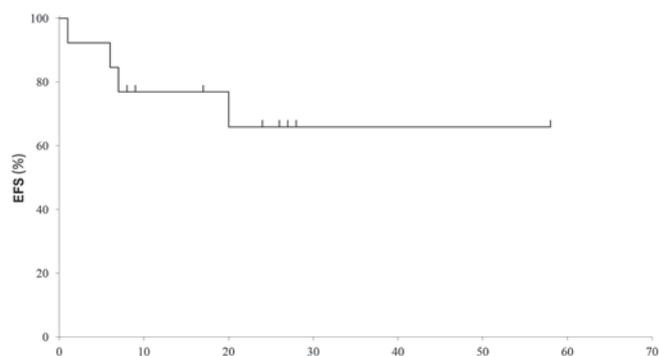


Figure 2. EFS following tyrosine kinase inhibitor treatment discontinuation. The 5-year EFS was 67% and the median duration of CMR was 20 months. EFS, event-free survival; CMR, complete molecular response.

event-free survival (EFS) was defined as the time from TKI discontinuation to molecular relapse (loss of CMR) or the date of the last molecular evaluation. These values were estimated using the Kaplan-Meier method. Statistical analysis was performed using a log-rank test. A P-value of  $\leq 0.05$  was considered to indicate statistically significant differences.

## Results

**Patient characteristics.** We evaluated a total of 46 newly diagnosed CML-CP patients who were treated with various TKIs and achieved CMR (Table I). The first-line TKI treatment was imatinib in 38, dasatinib in 6 and nilotinib in 2 patients. Prior to TKI treatment, additional cytogenetic abnormalities were detected by G-band analysis in 2 patients. With a median follow-up of 66 months, the 8-year OS rate of all the patients was 83% (Fig. 1). There was no significant difference in the OS rate between patients who continued (86%) and those who discontinued TKI treatment (100%).

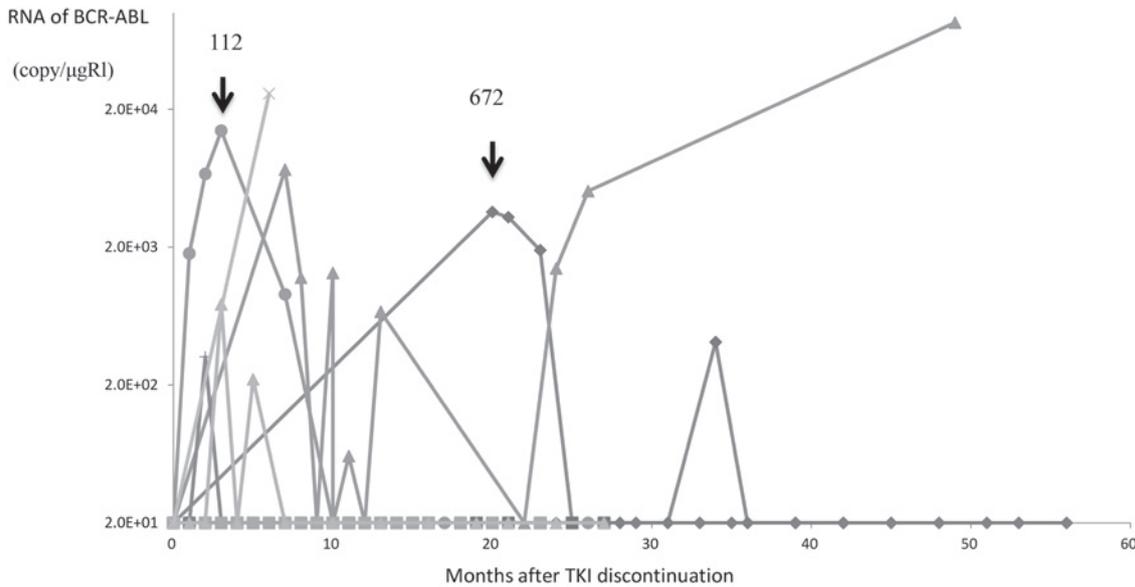


Figure 3. Time course analysis of BCR-ABL levels in patients who discontinued TKI treatment. TKI treatment was resumed in 2 patients (arrows). A total of 6 patients lost CMR: 2 patients were re-administered TKIs, 2 spontaneously attained a second CMR without retreatment and 2 remained in CHR without retreatment. TKI, tyrosine kinase inhibitor; CMR, complete molecular response.

Table III. Patient outcome.

Outcome	On TKIs (n=33)	Off TKIs (n=13)
Median follow-up, months (range)	34 (1-143)	107 (44-177)
Median follow-up after TKI discontinuation, months (range)	-	28 (10-60)
Disease status		
First CMR	20	7
Second CMR	1	4
CHR	11	2
Disease progression	1	0
Cause of death	4	0
Lung cancer	1	
Pulmonary infarction	1	
Uterine cancer	1	
CML blast crisis	1	

TKI, tyrosine kinase inhibitor; CMR, complete molecular response; CHR, complete hematological response; CML, chronic myeloid leukemia.

**Characteristics of patients who discontinued TKI treatment.** In patients who discontinued TKIs, the median duration of the treatment until discontinuation was 74 months (range, 27-158 months) (Table II). The reasons for treatment discontinuation were as follows: A total of 5 patients were unable to receive TKIs due to surgery (1 for a traffic accident and 4 for malignancy) and refused TKI treatment after recovery. The remaining 8 patients declined TKI treatment due to their high cost.

**Patient outcomes.** The median follow-up of the patients after TKI discontinuation was 28 months (range, 10-60 months) (Table III). The 5-year EFS was 67% and the median duration of CMR was 20 months (range, 1-60 months) (Fig. 2).

Of the 13 patients who discontinued TKIs, 7 remained in CMR with a median follow-up of 26 months (range, 10-60 months) (Table III), whereas the remaining 6 patients lost CMR, with a median follow-up of 29.5 months (range, 10-52 months). The median time to CMR loss after TKI discontinuation was 6.5 months (range, 1-20 months). The BCR-ABL levels after TKI discontinuation are presented in Fig. 3. Of the 6 patients who lost CMR, 2 were re-treated with TKIs and attained a second CMR; 2 spontaneously attained a second CMR without TKI treatment; and the remaining 2 patients lost CMR but remained in CHR without any treatment for 43-126 months. A total of 4 patients on TKI treatment who succumbed to the disease were aged >75 years, of whom 2 patients had solid cancers (lung cancer, n=1; and uterine cancer, n=1); for these 2 patients, the spleen size was not measured at diagnosis, so the Sokal or Hasford scores could not be calculated. The remaining 2 patients were classified as a high-risk Sokal score group; in 1 patient, severe thrombocytosis was found at diagnosis and led to pulmonary infarction and death; the other patient was unresponsive to all types of TKIs, developed a blast crisis and succumbed to CML. There were no mortalities among patients who discontinued TKI treatment.

**Discussion**

TKI discontinuation has been investigated in a number of clinical trials in CML patients who have been in CMR. In a study by Rousselot *et al* (9), where imatinib was discontinued in patients who had been in CMR for >2 years (range, 26-45 months), approximately half of the patients experienced a molecular relapse within 6 months following discontinuation.

No late relapse was observed 4 years after TKI discontinuation. In the Stop Imatinib (STIM) study, 61% of the patients lost CMR, mostly within the first 6 months following treatment discontinuation (15). The predictive factors for treatment-free remission are the Sokal score and the length of the imatinib treatment (12,15-17). However, the Sokal score could not be analysed, as the spleen size on admission was not recorded for all the patients in this study.

In our study, the probability of CMR persistence was 41%. The OS in patients who discontinued TKI treatment in our study almost equaled that in prospective TKI stop studies (15,18-20). Interestingly, no statistical differences in OS were observed between patients who continued and those who discontinued TKI treatment in our analysis, suggesting that survival was not always compromised by molecular relapse following TKI discontinuation, even without TKI re-treatment.

A total of 2 patients spontaneously attained a second CMR without TKI treatment, and 2 patients remained in CHR without any treatment for 43 and 126 months. These findings suggest that immediate re-treatment with TKIs may not always be necessary for patients who had been in CMR for >2 years and lost CMR following TKI discontinuation. This study was conducted retrospectively using a single-center analysis, which raises the risk of bias; thus, additional investigation is required to elucidate this issue.

## References

- Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J and Lydon NB: Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 2: 561-566, 1996.
- Deininger MW, Goldman JM and Melo JV: The molecular biology of chronic myeloid leukemia. *Blood* 96: 3343-3356, 2000.
- O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, *et al*; IRIS Investigators: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 348: 994-1004, 2003.
- Colombat M, Fort MP, Chollet C, Marit G, Roche C, Preudhomme C, Reiffers J, Praloran V and Mahon FX: Molecular remission in chronic myeloid leukemia patients with sustained complete cytogenetic remission after imatinib mesylate treatment. *Haematologica* 91: 162-168, 2006.
- Branford S, Seymour JF, Grigg A, Arthur C, Rudzki Z, Lynch K and Hughes T: BCR-ABL messenger RNA levels continue to decline in patients with chronic phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria. *Clin Cancer Res* 13: 7080-7085, 2007.
- Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silver RT, Goldman JM, Stone RM, *et al*; IRIS Investigators: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355: 2408-2417, 2006.
- Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, *et al*: Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia* 26: 2197-2203, 2012.
- Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, Wang J, Ipiña JJ, Kim DW, Ogura M, *et al*: Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 119: 1123-1129, 2012.
- Rousselot P, Huguot F, Rea D, Legros L, Cayuela JM, Maarek O, Blanchet O, Marit G, Gluckman E, Reiffers J, *et al*: Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood* 109: 58-60, 2007.
- Ross DM, Grigg A, Schwarzer A, Arthur C, Loftus K, Mills AK, *et al*: The majority of chronic myeloid leukemia patients who cease imatinib after achieving a sustained complete molecular response (CMR) remain in CMR, and any relapses occur early. *Blood (ASH Annual Meeting abstracts)* 112: 402-403, 2008.
- Mahon FX, Rea D, Guilhot F, Legros L, Guilhot J, Aton E, Dulucq S, Reiffers J and Rousselot P: Persistence of complete molecular remission in chronic myeloid leukemia after imatinib discontinuation: Interim analysis of the STIM trial. *J Clin Oncol (May 20 Supplement)* 27: 2009.
- Ross DM and Hughes TP: How I determine if and when to recommend stopping tyrosine kinase inhibitor treatment for chronic myeloid leukaemia. *Br J Haematol* 166: 3-11, 2014.
- Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, *et al*; European LeukemiaNet: Chronic myeloid leukemia: An update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 27: 6041-6051, 2009.
- Gabert J, Beillard E, van der Velden VHJ, Bi W, Grimwade D, Pallisgaard N, Barbany G, Cazzaniga G, Cayuela JM, Cavé H, *et al*: Standardization and quality control studies of 'real-time' quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia-A Europe Against Cancer Program. *Leukemia* 17: 2318-2357, 2003.
- Mahon FX, Réa D, Guilhot J, Guilhot F, Huguot F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, *et al*; Intergroupe Français des Leucémies Myéloïdes Chroniques: 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: 1029-1035, 2010.
- Yhim HY, Lee NR, Song EK, Yim CY, Jeon SY, Shin S, Kim JA, Kim HS, Cho EH and Kwak JY: Imatinib mesylate discontinuation in patients with chronic myeloid leukemia who have received front-line imatinib mesylate therapy and achieved complete molecular response. *Leuk Res* 36: 689-693, 2012.
- Ross DM, Bartley PA, Goyne J, Morley AA, Seymour JF and Grigg AP: Durable complete molecular remission of chronic myeloid leukemia following dasatinib cessation, despite adverse disease features. *Haematologica* 96: 1720-1722, 2011.
- Ross DM, Branford S, Seymour JF, Schwarzer AP, Arthur C, Bartley PA, Slader C, Field C, Dang P, Filshie RJ, *et al*: Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia* 24: 1719-1724, 2010.
- Mahon FX, Nicolini FE, Noel MP, Escoffre M, Charbonnier A, Rea D, Dubruille V, Varet BR, Legros L, Guerci A, *et al*: Preliminary report of the STIM2 study: A multicenter stop imatinib trial for chronic phase chronic myeloid leukemia *de novo* patients on imatinib. *Blood* 122: 654, 2013.
- Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, Gradembas M, Etienne G, Rea D, Roy L, *et al*: Loss of major molecular kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol* 32: 424-430, 2014.