International Journal of Hematology (2020) 112:41–45
https://doi.org/10.1007/s12185-020-02880-3

ORIGINAL ARTICLE

Assessment of estimated glomerular filtration rate in patients with chronic myeloid leukemia following discontinuation of tyrosine kinase inhibitors

Sho Okamoto[1,2] · Hiroshi Ureshino[1,3] · Atsushi Kawaguchi[4] · Motoaki Miyazono[5] · Yuji Ikeda[5] · Shinya Kimura[1,3]

Received: 11 January 2020 / Revised: 2 April 2020 / Accepted: 3 April 2020 / Published online: 18 April 2020

Abstract

BCR-ABL1 tyrosine kinase inhibitors (TKIs) have dramatically improved survival outcomes in patients with chronic phase chronic myeloid leukemia (CML-CP) and are associated with a manageable safety profile. However, long-term TKI administration can lead to cardiovascular or renal adverse events. One goal in discontinuation of TKIs was reduction of adverse events, but it is unclear whether chronic toxicities are ameliorated as a result. In this study, we evaluated changes in estimated glomerular filtration rate (eGFR) in patients with CML-CP before and after TKI discontinuation. Long-term TKI treatment appears to induce renal toxicity, as eGFR at the time of TKI discontinuation correlated with the duration of TKI treatment ($r=-0.478$, $p=0.005$). Patients who received imatinib as first-line treatment exhibited lower eGFR levels than those treated with dasatinib or nilotinib, which may be correlated with long-term treatment ($p=0.027$). After TKI discontinuation, no significant increases in eGFR were seen either in patients with treatment-free remission (66.8–71.2 ml/min/1.73 m^2) or molecular relapse (64.8–68.7 ml/min/1.73 m^2, $p=0.666$). These data indicate that TKI-induced renal toxicities are associated with long-term TKI treatment, and may be irreversible even following treatment discontinuation.

Keywords Chronic myeloid leukemia · Renal toxicities · Imatinib · Dasatinib · Nilotinib

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that results from aberrant clonal hematopoietic stem cells caused by oncogenic BCRABL fusion protein, which arises from a t(9;22)(q34;q11) chromosomal translocation (Philadelphia chromosome) [1]. BCR-ABL1 tyrosine kinase inhibitors (TKIs) have significantly improved survival outcomes in patients with chronic phase CML (CML-CP), and approximately 50% of patients who achieved a sustained deep molecular response (DMR) can discontinue TKI administration without molecular relapse [2]. However, long-term TKI treatment may be required, with the majority of TKI stop studies showing that approximately 70–100 months of treatment is required before TKI therapy can be discontinued [3–10]. Although TKIs are associated with relatively good safety profiles, adverse events such as renal toxicity and cardiovascular events are often observed with long-term TKI use [11]. In CML-CP clinical trials, one reason for discontinuing TKI treatment is to relieve patients from the adverse effects of long-term TKI use, although it is unclear whether these chronic adverse toxicities are reduced or resolved after discontinuation. Here, a retrospective evaluation has been conducted to determine changes in estimated glomerular filtration rate (eGFR) in patients with CML-CP who discontinued TKI treatment.

✉ Hiroshi Ureshino
m00010hu@jichi.ac.jp

1 Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

2 Department of Internal Medicine, Saga-Ken Medical Centre Koseikan, Saga, Japan

3 Department of Drug Discovery and Biomedical Sciences, Faculty of Medicine, Saga University, Saga, Japan

4 Center for Comprehensive Community Medicine, Faculty of Medicine, Saga University, Saga, Japan

5 Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan

Patients and methods

Patients

This retrospective analysis was conducted at Saga University Hospital (Saga, Japan); eGFR was evaluated in patients with CML-CP patients who received imatinib, dasatinib, or nilotinib as first-line treatment and who achieved sustained DMR, subsequently discontinuing TKI therapy between December 2001 and March 2017. Patients who were lost to follow-up, those who had no available laboratory data, and those enrolled in other clinical trials were excluded. The final follow-up date was June 2019. All clinical data were reviewed by two expert hematologists.

The study protocol was approved by the institutional review board of Saga University. All procedures involving human participants were conducted in accordance with the ethical standards of institutional and/or national research committees, and the Declaration of Helsinki. Informed consent was waived because of the retrospective design of the data collection. Information of the research, including the aims of use of specimens and the opportunity to opt out from the research, was made public. No patients objected to this study.

Definitions

Real-time quantitative reverse transcription polymerase chain reaction analysis was performed to detect the *BCR-ABL1* mRNA transcript level. DMR was defined as *BCR-ABL1* transcript level $\leq 0.01\%$ on the standardized international scale (IS). A major molecular response (MMR) was defined as a *BCR-ABL1* IS transcript level $\leq 0.1\%$. Treatment-free remission (TFR) was defined as sustained DMR in the absence of treatment. Molecular relapse (M-Rel) was defined as the loss of DMR ($0.01\% > \text{IS}$) at two consecutive time points or loss of MMR ($0.1\% > \text{IS}$) at a single time point; in these cases, the patient was re-treated with the last TKI at the previously effective dose.

Statistical analyses

The eGFR was estimated using the Cockcroft–Gault method at 3 timepoints before and after TKI discontinuation. All continuous variables (age, treatment duration, follow-up duration, complete cell counts, eGFR change or eGFR at TKI discontinuation) were compared between patients who achieved TFR and those exhibiting M-Rel using Mann–Whitney *U* tests. As patients with M-Rel were re-treated with a TKI immediately after relapse, these subjects were defined as patients who received continuous TKI treatment; all molecular relapses occurred within 6 months of TKI discontinuation. Fisher's exact tests were used to compare clinical features (sex, hypertension [HT], hyperlipidemia [HL], diabetes mellitus [DM], and first-line TKIs) in the TFR and M-Rel groups. Pearson's correlation analysis was used to determine the correlation between eGFR and TKI treatment duration, between eGFR and age at diagnosis, and between age at diagnosis and TKI treatment duration. Paired *t* tests or repeated-measures analysis of variance (ANOVA) were used to detect differences in eGFR across multiple test data. Multiple regression analysis was performed to determine the factors involved in the decline of eGFR at the time of TKI stop (Variables included in the analysis were type of first-line TKIs and TKI treatment duration). Two-sided p values of < 0.05 were considered statistically significant. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University) [12].

Results

Patient characteristics

Data from 33 patients with CML-CP were included in the analysis (17 males, 16 females). The clinical characteristics of the patients are summarized in Table 1. The median age at diagnosis was 56 years (range, 35–82 years). First-line TKIs were imatinib (IMA, $n = 17$), dasatinib (DAS, $n = 11$), and nilotinib (NIL, $n = 5$); TKIs used prior to discontinuation were IMA ($n = 5$), DAS ($n = 22$), and NIL ($n = 6$). Median dose of IMA, DAS, and NIL per day were 300 mg (range, 150–300 mg), 20 mg (10–100 mg) and 600 mg (all patients received 600 mg of nilotinib), respectively. The median duration of TKI administration was 4.97 years (range, 2.56–13.89 years), and the median follow-up time from diagnosis was 8.47 years (range, 5.11–17.18 years). A total of 21 patients experienced TFR and 12 experienced M-Rel. Fewer male patients experienced M-Rel (male: 2/17, female: 10/16, $p = 0.004$). Other clinical features did not differ between the TFR and M-Rel groups, including underlying disease-associated chronic kidney disease (CKD) and eGFR level at diagnosis.

Changes in eGFR following TKI discontinuation

At the time of TKI discontinuation, a statistically significant correlation was seen between eGFR and the duration of TKI treatment ($r = -0.478$, $p = 0.005$; Fig. 1). Evaluation of the average eGFR at 3 timepoints (at 3 years before TKI discontinuation, at TKI discontinuation and at 2 years after TKI discontinuation) showed a moderate decline in the 3 years prior to TKI discontinuation, which was similar in both the

Table 1 Data are presented at median [range] or *N* (%)

	Overall *N*=33	Patients with TFR *N*=21	Patients with M-rel *N*=12	*p* Value
Age at diagnosis (years)	56 (35–82)	55 (35–82)	57.5 (46–78)	0.33
Sex				
Male/Female	17/16 (51.5%/48.5%)	15/6	2/10	0.004
First line TKI				
Imatinib	17 (51.5%)	11 (52.4%)	6 (50.0)	1.00
Dasatinib	11 (33.3%)	6 (28.6%)	5 (42.0%)	
Nilotinib	5 (15.2%)	4 (19.0%)	1 (8.0%)	
Last TKI before discontinuation				
Imatinib	5 (15.2%)	5 (23.8%)	0 (0%)	0.067
Dasatinib	22 (66.2%)	11 (52.4%)	11 (91.7%)	
Nilotinib	6 (18.2%)	5 (23.8%)	1 (8.3%)	
Dose of TKI (mg/day)				
Imatinib	300 (150–400)	300 (150–300)	350 (300–400)	0.333
Dasatinib	20 (10–100)	30 (20–100)	20 (10–50)	0.277
Nilotinib	600 (600–600)	600 (600–600)	600 (600–600)	
CKD risk factors (HT, HL or DM)				
0	24 (72.7%)	13 (61.9%)	11 (91.7%)	0.199
1	5 (15.2%)	5 (23.8%)	0 (0%)	
2	3 (9.1%)	2 (9.5%)	1 (8.3%)	
3	1 (3.0%)	1 (4.8%)	0 (0%)	
WBC (10^3/μL)	20.90 (8.16–290.00)	24.40 (11.00–208.40)	18.25 (8.16–290.00)	0.302
Hb (g/dL)	13.6 (5.9–16.4)	14.3 (5.9–16.4)	13.2 (10.1–15.4)	0.110
PLT (10^3/μL)	553.5 (182.0–2032.0)	562.5 (223.0–2032.0)	537.5 (182.0–1169.0)	0.243
TKI treatment duration until stop (years)	4.97 (2.56–13.89)	4.97 (3.09–13.89)	5.37 (2.56–8.56)	0.575
Total follow up duration (years)	8.47 (5.11–17.18)	8.74 (5.52–17.18)	8.40 (5.11–13.75)	0.477
eGFR change in 3 years before stop (mL/min/1.73m^2)	− 1.76 (− 6.87 to 7.05)	− 1.46 (− 6.87 to 3.60)	− 2.25 (− 6.87 to 7.05)	0.726
eGFR change in 2 years after stop (mL/min/1.73m^2)	0.90 (− 23.80 to 13.87)	1.70 (− 23.80 to 9.40)	0.12 (− 5.40 to 13.87)	1.00
eGFR at stop (mL/min/1.73m^2)	65.30 (41.1–95.8)	67.95 (41.5–87.8)	65.30 (41.1–95.8)	0.708

*Statistically significant

CKD chronic kidney disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *HL* hyperlipidemia, *HT* hypertension, *M-Rel* molecular relapse, *PLT* platelet count, *TKI* tyrosine kinase inhibitor, *TRF* treatment-free remission, *WBC* white blood cell count, *eGFR* estimated glomerular filtration

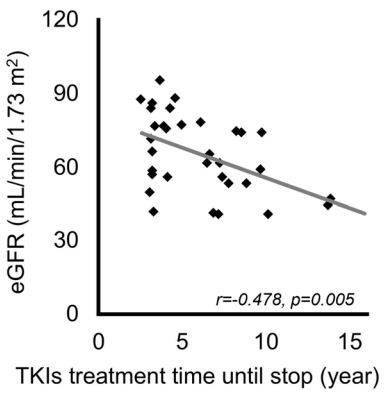

Fig. 1 Correlation between estimated glomerular filtration (eGFR) at tyrosine kinase inhibitor (TKI) stop and TKI treatment time

TFR and M-Rel groups (− 1.46 vs − 2.25 ml/min/1.73m^2; $p = 0.726$; Table 1). A slight increase in mean eGFR was seen in patients with both TFR after TKI discontinuation and in patients with M-Rel (+ 0.70 vs + 0.12 ml/min/1.73m^2; $p = 1.000$; Table 1), whereas the increase was not statistically significant in either group ($p = 0.666$). In addition, no significant differences in eGFR were seen between the TFR and M-Rel groups (67.95 vs 65.30 ml/min/1.73m^2; $p = 0.708$; Table 1).

Changes in eGFR according to first-line TKI

The use of first-generation imatinib or second-generation dasatinib or nilotinib was evaluated to determine any differences in the effect on eGFR. Data showed that eGFR levels in patients who received imatinib as initial treatment

were significantly lower than those seen in patients treated with dasatinib or nilotinib ($p = 0.027$). The time effect on the differences in eGFR was not statistically significant by repeated-measures ANOVA. The duration of TKI treatment was significantly longer in patients receiving imatinib than in patients receiving dasatinib or nilotinib (mean ± standard deviation, 8.13 ± 2.87 years vs. 3.82 ± 1.00 years, respectively; *t* test, $p < 0.001$).

Multiple regression analysis on eGFR at the time of TKI discontinuation

We additionally performed multiple regression analysis to determine the factors involved in the decline of eGFR at the time of TKI stop. Multiple regression analysis revealed eGFR at TKI stop was inversely correlated with treatment duration (coefficient − 2.56, $p = 0.038$), while the type of TKI was not (coefficient 0.835, $p = 0.908$).

Discussion

Here, we report eGFR changes in patients with CML over a 5-year period before and after TKI discontinuation. The proportion of patients who maintained TFR after cessation of TKIs (64%) was consistent with previous studies [3–9, 13]. Fewer male patients developed molecular relapse, which is consistent with the results of the 'Stop Imatinib' (STIM) trial [3], although male sex has not been seen to be a favorable predictive factor for TFR in other TKI stop studies [3–9, 13]. Female sex has previously been reported to be an independent favorable factor for DMR [14–16]. The existence of sex-specific responses in patients with CML-CP may, therefore, be supported by these clinical observations, but detailed mechanisms have not been fully elucidated, and further investigation is required.

In the present study, TKI treatment duration was seen to correlate with eGFR decline, which is consistent with previous reports [17–20]. The average eGFR decline until TKI discontinuation was seen to be 1.76 ml/min/1.73 m^2/year. Although it is difficult to compare these results with those seen in previous studies, it appears that eGFR levels in the present patient group decreased more rapidly than that seen in healthy Japanese individuals (< 1.0 ml/min/1.73 m^2/year) [21, 22]. These results indicate that long-term TKI treatment can induce a decline in eGFR in patients with CML-CP.

Patients who received first-line treatment with imatinib showed lower eGFR levels than patients treated with dasatinib or nilotinib, possibly due to the longer treatment duration associated with imatinib [17, 23]. Imatinib was the first TKI approved for the treatment of CML-CP in Japan in 2001; nilotinib and dasatinib were approved as first-line treatment approximately 10 years later [24]. These second-generation TKIs are stronger inhibitors of BCR-ABL than imatinib, and DMR can be achieved with a shorter treatment duration [25–27]. Therefore, the imatinib treatment duration may be significantly longer than dasatinib or nilotinib, leading to a greater incidence of renal toxicities, as observed in this study. The present study showed no significant increase in eGFR at the 2-year timepoint following TKI discontinuation. This follow-up period may be short in comparison with the treatment duration (approximately 5 years) and, therefore, may not be long enough to demonstrate a change in eGFR.

In conclusion, TKI-induced renal toxicities were associated with long-term TKI treatment time, while may be irreversible even following treatment discontinuation.

Acknowledgements None.

Funding This work was supported by research grants from JSPS KAKENHI (19K17860, HU) and JSPS KAKENHI (17K09908, SK).

Compliance with ethical standards

Conflict of interest SK has received honoraria from Bristol-Myers Squibb, Novartis, Pfizer, and Otsuka Pharmaceuticals, and research funding from Bristol-Myers Squibb, Novartis, Pfizer, Otsuka Pharmaceuticals, and Ohara Pharmaceuticals. The other authors declare no potential conflicts of interest.

Ethical approval This study was approved by the Institutional Review Board of Saga University. All procedures involving human participants were performed in accordance with the ethical standards of institutional and/or national research committees, and the Declaration of Helsinki.

Informed consent Informed consent was waived because of the retrospective design of the data collection. Information of the research, including the aims of use of specimens and the opportunity to opt out from the research, was made public. No patients objected to this study.

References

1. Ureshino H, Shindo T, Kimura S. Role of cancer immunology in chronic myelogenous leukemia. Leuk Res. 2020;88:106273.
2. Kimura S. Current status of ABL tyrosine kinase inhibitors stop studies for chronic myeloid leukemia. Stem Cell Investig. 2016;3:36–36.
3. Mahon F-X, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. 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. 2010;11:1029–35.
4. Imagawa J, Tanaka H, Okada M, Nakamae H, Hino M, Murai K, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. Lancet Haematol. 2015;2:e528–e535535.
5. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: Results from the ENESTfreedom study. Leukemia. 2017;31:1525–31.

6. Mahon F-X, Boquimpani C, Kim D-W, Benyamini N, Clementino NCD, Shuvaev V, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, Open-Label Study. Ann Intern Med. 2018;168:461–70.
7. Fujisawa S, Ueda Y, Usuki K, Kobayashi H, Kondo E, Doki N, et al. Feasibility of the imatinib stop study in the Japanese clinical setting: delightedly overcome CML expert stop TKI trial (DOMEST Trial). Int J Clin Oncol. 2019;24:445–53.
8. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. 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. 2018;19:747–57.
9. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood. 2017;129:846–54.
10. Takahashi N, Tauchi T, Kitamura K, Miyamura K, Saburi Y, Hatta Y, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. Int J Hematol. 2018;107:185–93.
11. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016;30:1648–71.
12. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transpl. 2013;48:452–8.
13. Okada M, Imagawa J, Tanaka H, Nakamae H, Hino M, Murai K, et al. Final 3-year results of the dasatinib discontinuation trial in patients with chronic myeloid leukemia who received dasatinib as a second-line treatment. Clin Lymphoma Myeloma Leuk. 2018;18(353–360):e1.
14. Breccia M, Molica M, Colafigli G, Massaro F, Quattrocchi L, Latagliata R, et al. Prognostic factors associated with a stable MR4.5 achievement in chronic myeloid leukemia patients treated with imatinib. Oncotarget. 2018;9:7534–40.
15. Branford S, Yeung DT, Ross DM, Prime JA, Field CR, Altamura HK, et al. Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML. Blood. 2013;121:3818–24.
16. Ureshino H, Shindo T, Kojima H, Kusunoki Y, Miyazaki Y, Tanaka H, et al. Allelic polymorphisms of *KIR* s and *HLA* s predict favorable responses to tyrosine kinase inhibitors in CML. Cancer Immunol Res. 2018;6:745–54.
17. Yilmaz M, Lahoti A, O'Brien S, Nogueras-González GM, Burger J, Ferrajoli A, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer. 2015;121:3894–904.
18. Marcolino MS, Boersma E, Clementino NCD, Macedo AV, Marx-Neto AD, Silva MHCR, et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. Ann Oncol. 2011;22:2073–9.
19. Ren X, Qin Y, Huang X, Zuo L, Jiang Q. Assessment of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase receiving tyrosine kinase inhibitors. Ann Hematol. 2019;98:1627–40.
20. Sakurai M, Kikuchi T, Karigane D, Kasahara H, Matsuki E, Hashida R, et al. Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia. Int J Hematol. 2019;109:292–8.
21. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
22. Baba M, Shimbo T, Horio M, Ando M, Yasuda Y, Komatsu Y, et al. Longitudinal study of the decline in renal function in healthy subjects. PLoS ONE. 2015;10:e0129036.
23. Malkan UY, Haznedaroglu IC. Discontinuation of imatinib mesylate could improve renal impairment in chronic myeloid leukemia. Open Med. 2019;14:22–4.
24. Kizaki M, Takahashi N, Iriyama N, Okamoto S, Ono T, Usui N, et al. Efficacy and safety of tyrosine kinase inhibitors for newly diagnosed chronic-phase chronic myeloid leukemia over a 5-year period: results from the Japanese registry obtained by the New TARGET system. Int J Hematol. 2019;109:426–39.
25. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044–54.
26. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, et al. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-Naïve chronic myeloid leukemia patients trial. J Clin Oncol. 2016;34:2333–400.
27. Kimura S, Imagawa J, Murai K, Hino M, Kitawaki T, Okada M, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2020;7:e218–e225225.