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ORIGINAL ARTICLE

Changes from imatinib mesylate to second generation tyrosine kinase inhibitors improve renal impairment with imatinib mesylate in chronic myelogenous leukemia

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Abstract Understanding adverse events in long-term tyrosine kinase inhibitor (TKI) therapy for chronic myelogenous leukemia (CML) is important. We investigated changes in renal function during TKI therapy for CML. We retrospectively analyzed levels of serum creatinine (sCrn) and values of estimated glomerular filtration rate (eGFR) from June 2001 to March 2015. Sixty patients initially treated with imatinib were enrolled in this study. Continuous variables of sCrn and eGFR were compared by paired student's *t* test. Median age or duration of treatment with imatinib was 49 years (range 19–81) or 101 months (range 8–165), respectively. Mean levels of sCrn or mean values of eGFR had increased or decreased 1 year later from start of imatinib throughout observation with statistical significance ($p < 0.05$), respectively. In 38 patients, the TKI used was changed from imatinib to a second-generation TKI (nilotinib: 32; dasatinib: 6) for various reasons. We observed statistically significant ($p < 0.05$) amelioration in mean levels of sCrn and values of eGFR after only 1 month following the changes to second-generation TKIs. These results suggest that imatinib has adverse effects on renal function and that changes from imatinib to a second-generation TKI should be considered as a therapeutic option in cases of renal impairment due to imatinib.

Keywords Chronic myelogenous leukemia · Imatinib · Renal impairment

Introduction

Tyrosine kinase inhibitors (TKIs) inhibit kinase activities of bcr-abl oncoprotein resulting from the reciprocal translocation between chromosomes 9 and 22 in chronic myelogeneous leukemia (CML). Imatinib mesylate (imatinib) is a first generation tyrosine kinase inhibitor and the introduction of imatinib has dramatically improved the prognosis of CML patients [1–3].

Treatment with TKIs have enabled CML patients to survive for a long time. It is very important to clarify adverse effects in long-term treatments with TKIs and to improve the quality of life in CML patients. So far, long-term observations on adverse effects exist especially in imatinib. It has been reported that diarrhea and hypophosphatasia were frequently observed shown as adverse events in long-term therapy with imatinib [3–5]. As for second generation TKIs, vascular adverse events, such as ischemic heart disease, ischemic cerebrovascular events, or peripheral arterial occlusive disease (PAOD) have been described as new type toxicities in CML patients treated with nilotinib hydrochloride hydrate (nilotinib) [6, 7]. In CA180-034 study, 30 % of patients treated with second-line dasatinib hydrate (dasatinib) manifested pleural effusions within 6 years [8]. Also, pulmonary hypertension was diagnosed in 1.2 % of patients in DASISION study after 2-year follow-up [9]. Thus, although the rate of incidence is relatively low, it has been reported that TKIs treatment result in adverse effects that significantly affect on the function of organs and quality of life in CML patients.

It has been reported that renal failure was reported as a rare event and was shown to occur in <1 % patients

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medicated with imatinib in the dose-escalating studies of chronic phase and blast crisis in CML [10, 11]. These reports showed that imatinib therapy could rarely be associated with potentially renal injury [10, 11]. On the other hand, two reports have recently shown that long-term treatment may cause clinically relevant decrease in the estimated gromerular filtration rate (eGFR) [12, 13].

Imatinib has inhibitory effects not only on bcr-abl activities but also on other tyrosine kinases, such as platelet-derived growth factor receptor (PDGF-R) and c-kit [14]. In fact, imatinib sufficiently inhibits kinase activities of PDGF-R ($IC_{50} = 72$ nM) and c-KIT ($IC_{50} = 99$ nM) rather than BCR-ABL ($IC_{50} = 221$ nM) [15]. It has been reported that PDGFR-α is widely expressed on renal interstitial cells and, to some extent, on mesangial cells and PDGFR-β is also expressed on mesangial cells, glomerular parietal epithelial cells, and interstitial cells [16]. These results suggest that imatinib might affect renal functions during the long-term treatment periods.

In this study, then, we focused on the renal functions after the treatment with imatinib for CML patients in chronic phase. And also, we analyzed the renal functions after the changes from imatinib to second generation TKIs.

Patients and methods

Sixty CML in chronic phase patients who had been initially treated with imatinib as first TKI were retrospectively analyzed from June 2001 to March 2015. All patients were diagnosed with CML through the presence of philadelphia positive chromosome.

We first examined sequential changes of the levels of sCrn and the values of eGFR after the start of imatinib therapy. Values of eGFR were calculated using the 3-variable Japanese equation as follows: eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female), proposed by Japanese Association of Chronic Kidney Disease Initiatives (J-CKDI) [17]. eGFR is usually estimated from serum creatinine, age, sex, and ethnicity with the Modification of Diet in Renal Disease (MDRD) Study equation [18]. However, there have always been concerns with the ethnicity coefficient since it does not address non-white, non-African American ethnic groups [19]. Therefore, J-CKDI generated the 3-variable Japanese equation as original equation for estimating GFR of Japanese patients. And this is the most commonly clinical formula in Japan [17].

Chronic renal disease (CKD) was defined as follows: estimated GFR persisted below 60 mL/min/1.73 m^2 for at least 90 days [20].

Renal functions were followed until March 2015 or the time of cessation of TKIs. In the cases, switched from imatinib to second generation TKIs, we also had examined the renal functions until March 2015.

With respect to the levels of sCrn or the values of eGFR, continuous variables were compared by paired Student's *t* test. *p* value of <0.05 was considered as statistically significant.

All data were analyzed using "EZR on R commander" statistical software (ver.1.27, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html) [21].

Results

Patients' characteristics

In total, 60 CML in chronic phase patients were enrolled in this study. Baseline characteristics are presented in Table 1. The median age at starting treatment with imatinib was 49 years (range 19–81), 38 patients (63.3 %) were male. The median duration of administration of imatinib was 101 months (range 8–165). In this study, five patients had kidney-related complications (renal rupture caused by traffic accident, chronic renal disease, IgA nephropathy, Gitelman syndrome) and there were 9 patients who contracted either hypertension or diabetes mellitus or hyperlipidemia at the initiation of imatinib. Thirty-two patients had none of the above-mentioned complications. Unfortunately, we were not able to obtain any data regarding these three complications in 19 patients. Additionally, there were 2 patients in whom imatinib were discontinued for the reason with renal impairment or patient's wish. Twenty-five patients (41.7 %) had received previous treatments before imatinib therapy but 35 patients (58.3 %) received no prior treatment. Out of twenty-five patients with previous

Table 1 Patients' characteristics at imatinib therapy ($N = 60$)

Characteristics	No.	%
Male	38	63.3
Age of diagnosis (year)		
Median	49	
Range	19–81	
Duration of administration with imatinib (months)		
Median	101	
Range	8–165	
Renal function at baseline		
Serum creatinine level		
Median	0.775	
Range	0.5–1.37	
eGFR		
Median	78.7	
Range	42.6–116.5	

treatments, three patients had received allogenic hematopoietic cell transplantation. Five patients were treated with hydroxyurea (HU), 3 patients with interferon-alpha (IFN), 11 patients with HU and IFN, 2 patients with IFN and busulfan (BU), and 1 patient treated with HU, IFN and BU. With regard to overall response of imatinib therapy, 47 of 60 patients (78.3 %) achieved a major molecular response, 12 of 60 patients (20 %) achieved a complete cytogenetic response and 1 patient had a complete hematological response.

At the start of imatinib, the value of median serum creatinine was 0.76 mg/dl (range 0.5–1.37 mg/dl) and median eGFR was 78.7 mL/min/1.73 m^2 (range 42.6–116.5 mL/min/1.73 m^2).

Sequential changes of renal functions after imatinib therapy

We showed the sequential data of renal function after the imatinib therapy as shown in Fig. 1. The average values of sCrn levels and eGFR at the start of imatinib were 0.79 mg/dl and 78.4 mL/min/1.73 m^2, respectively. sCre levels was gradually increasing after the treatment and showed statistically significant difference compared to initial levels after 1 year following the start of imatinib ($p < 0.05$) (Fig. 1a). In general, age and gender possibly affect on the levels of sCrn. Then we examined the sequential data of eGFR after imatinib therapy. Decrease of eGFR had been observed with statistically significant difference from 1 year ($p < 0.05$) (Fig. 1b). Increase of sCrn and decrease of eGFR had been shown throughout our observation periods. After 10 years following imatinib therapy, average values of sCrn levels and eGFR were 1.20 mg/dl and 56.2 mL/min/1.73 m^2, respectively.

Nine patients were treated for hypertension and/or diabetes mellitus and/or hyperlipidemia at the initiation of imatinib. In contrast, 32 patients had not manifested the above-mentioned complications throughout the observation period. Interestingly, average values of sCrn and levels of eGFR were getting worse from 1 year with statistically significant differences whether patients had these three complications or not (data not shown).

One patient who had discontinued imatinib for the reason with renal failure showed the exacerbation of renal function even after the cessation of imatinib. In the other patient, imatinib was stopped at the patient's request and the values of sCrn and levels of eGFR were not changed after the discontinuation.

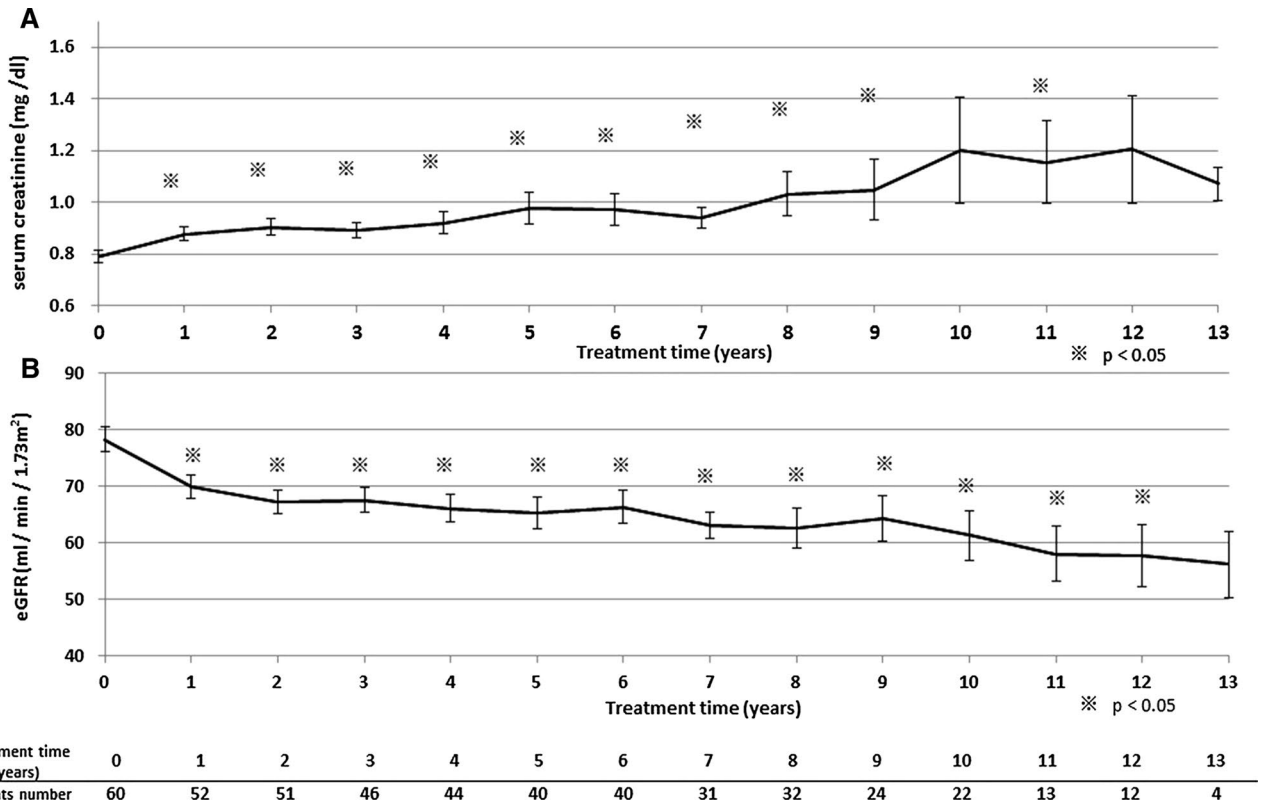

Fig. 1 Sequential changes with levels of sCrn (**a**) and values of eGFR (**b**) during the long-term imatinib therapy. Statistically significant difference was calculated with paired Student's *t* test between the baseline and each time point. *Asterisk* (*) indicates $p < 0.05$

Table 2 Patients' characteristics at the second generation tyrosine kinase inhibitors therapy ($N = 38$)

	Nilotinib ($N = 32$)		Dasatinib ($N = 6$)	
	No.	%	No.	%
Male	18	58.1	2	33.3
Age of starting treatment (year)				
Median	57		46	
Range	25–84		31–60	
Duration of administration with the second generation TKIs (month)				
Median	31		37	
Range	4–72		10–64	
Reason for change (imatinib mesylate to the second generation TKIs)				
Adverse effect	12	38.7	2	33.3
Insufficiency	7	16.1	2	33.3
Patients wish	12	3.2	1	16.7
Unknown	1	3.2	1	16.7

These results showed that the treatment with imatinib for CML could gradually deteriorate renal functions from 1 year after the start of treatment.

Influences of previous treatments before imatinib on renal impairment

In our study, 25 patients had received previous therapies including HU, BU, IFN and allogeneic hematopoietic cell transplantation before imatinib therapy. We had to consider the possibilities that the previous treatments might affect on the renal function after the treatment of imatinib. We then compared the sequential data of renal functions between the patients in the presence or absence with previous treatments. The average values of sCrn levels had concomitantly increased in both two groups for 5 years and statistically significant difference were not observed in two groups (Supplemental Fig. 1A). As with the levels of sCrn, the average values of eGFR have been exacerbated in both two groups and statistically significant differences were not observed in two groups (Supplemental Fig. 1B).

These results suggest that the previous treatments do not affect on renal functions after imatinib therapy.

Influence of changes from imatinib to second generation TKIs on renal functions

In this study, 38 patients could not continue imatinib treatment because of intolerances, insufficiencies or clinical trials. As shown in Table 2, 32 patients exchanged TKI from imatinib to nilotinib and 6 patients did to dasatinib.

Median age in nilotinib or dasatinib group were 57 years (range 24–84) or 46 years (range 31–60), respectively. Median treatment duration in nilotinib or dasatinib group was 31 months (range 4–72 months) or 37 months (range 10–64 months), respectively. The changes from imatinib to second generation TKIs had been performed as following situations: adverse effects (14 patients), insufficiencies (9 patients), patient's wishes (13 patients), unknown (2 patients).

Then we examined whether the change from imatinib to nilotinib or dasatinib had any effects on renal functions. As shown in Fig. 3, the average values of sCrn levels had improved from a month to 3 years after the exchange to the second generation TKI with statistical significance in comparison with that at the time of exchange to second TKIs ($p < 0.05$) (Fig. 2a). Same as sCrn levels, the average values of eGFR had improved from a month to 3 years after the change to second generation TKIs with statistical significance ($p < 0.05$) (Fig. 2b).

These results suggest that second generation TKIs might be less toxic on renal functions than imatinib, and show the possibilities that the change from imatinib to second generation TKIs could improve the renal functions impaired by imatinib.

Even in the patients with CKD, changes from imatinib to second generation TKIs improved the decrease of eGFR

Chronic renal disease (CKD) was defined as follows: estimated GFR persisted below 60 mL/min/1.73 m^2 for at least 90 days. In our study, twenty-three patients developed new-onset CKD over the course of imatinib therapy, excepted two patients who had a prior diagnosis of CKD at the start of imatinib therapy. Sixteen out of twenty-three new-onset CKD patients changed TKI from imatinib to second generation TKIs (nilotinib: fourteen patients, dasatinib: two patients).

Then, we likewise examined whether the change of TKIs could improve the decrease of eGFR about new-onset CKD patients. As shown in Fig. 3, the average values of eGFR had improved with statistical significant difference in comparison with those at the time of changes of TKIs in new-onset CKD patients ($p < 0.05$) (Fig. 3).

Furthermore, in 8 out of 16 new-onset CKD patients, treated with second generation TKIs, the average values of eGFR had increased over 60 mL/min/1.73 m^2.

These results suggest that change of TKIs could improve renal functions even in CKD patients triggered by imatinib.

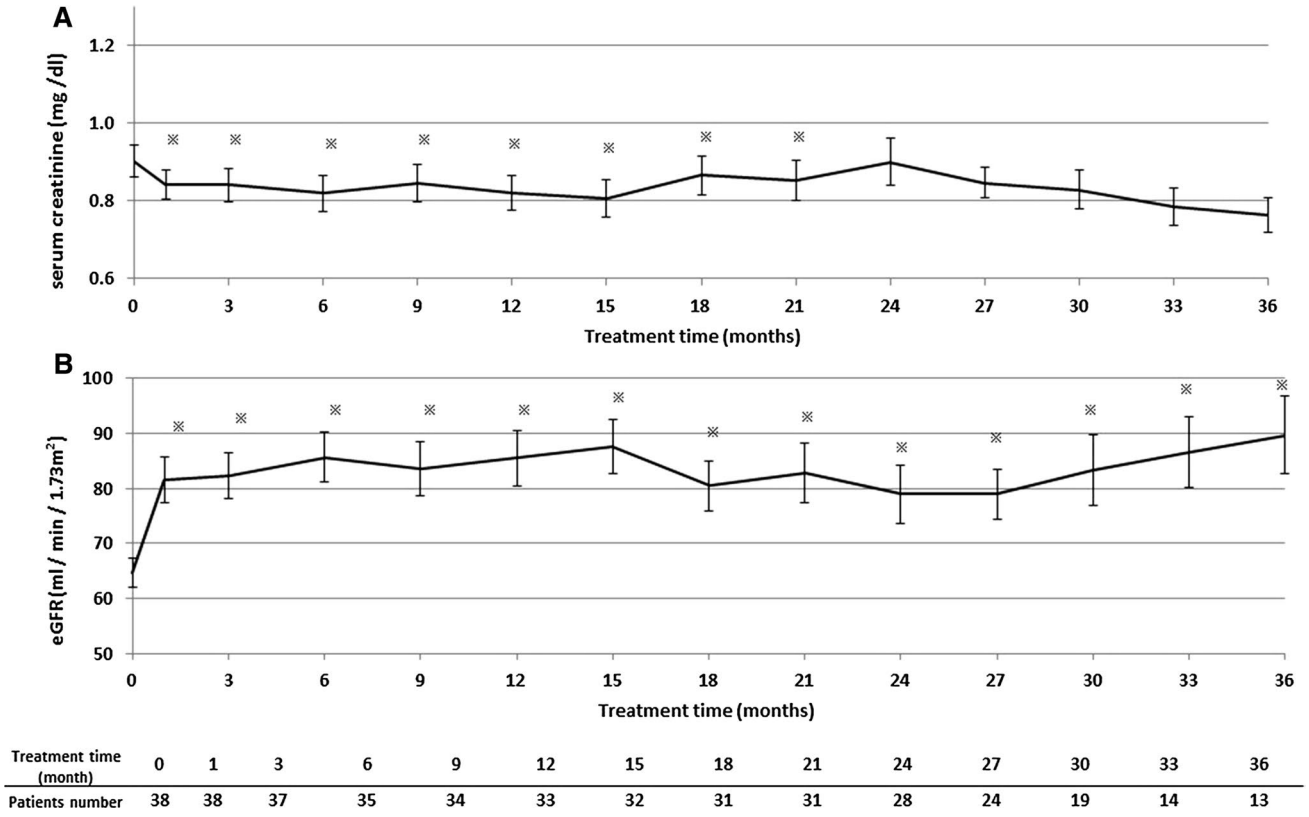

Fig. 2 Effects of changes from imatinib to second generation TKIs on renal functions. The levels of sCrn (**a**) and values of eGFR (**b**) following exchanges from imatinib to second generation TKIs (nilotinib and dasatinib) were shown. Statistically significant difference was calculated with paired Student's *t* test between the baseline and each time point. *Asterisk* (*) indicates $p < 0.05$

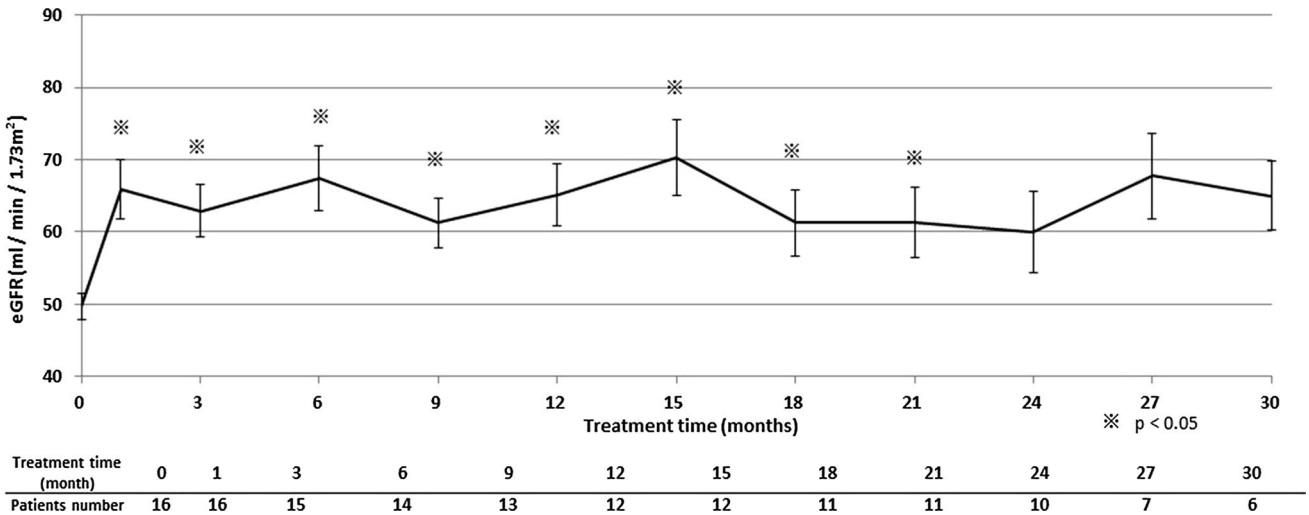

Fig. 3 Changes from imatinib to second generation TKIs improved the decrease of eGFR even in new-onset CKD patients. Sequential changes with values of eGFR following exchanges from imatinib to second generation TKIs (nilotinib and dasatinib) was shown in new-onset CKD patients. Statistically significant difference was calculated with paired Student's *t* test between the baseline and each time point. *Asterisk* (*) indicates $p < 0.05$

Discussion

Our study had two major findings. First, our study suggests that the treatment for CML with imatinib could get gradually worse both the levels of sCrn and eGFR. There are only two reports that analyzed the renal functions in patients receiving the treatment with long-term imatinib [12, 13]. Marcolino et al. have reported that the long-term treatment with imatinib may cause clinically relevant decrease in eGFR that may lead to chronic renal failure [12]. Musa Yilmaz et al. examined the effects of three TKIs on renal functions in newly diagnosed CML patients. They reported that imatinib decreased eGFR after the treatment, but other two TKIs, nilotinib and dasatinib, did not impair renal functions [13]. Both two previous reports have shown that imatinib therapy for CML could induce decrease of eGFR in accordance with our study. In contrast with previous reports, our study has contained the patients treated with previous therapy. Because significant differences in renal functions had not been observed between patients in the presence or the absence with previous treatment, we judged that the presence of previous treatments before imatinib should not affect the results in our study.

Second, our study also demonstrated that the change from imatinib to second generation TKIs could improve renal functions impaired by imatinib therapy. The improvements of renal functions had been observed 1 month after the change of TKI. Moreover, even in new-onset CKD patients caused by the imatinib therapy, the change of TKI from imatinib to second TKIs could repair renal functions.

The molecular mechanisms of decrease in eGFR caused by imatinib have not been fully elucidated. However, a few reports have suggested that the toxic effects of imatinib may be related to the inhibition of PDGF-R signaling [14]. The PDGF-R is expressed on glomerulus, arteries, tubules and interstitiums in renal cells [16]. PDGF-β/PDGF-R axis could be significantly involved in renal tubular cell regeneration after acute tubular necrosis in animal models [22]. In addition, inhibition of PDGF-β/PDGF-R axis could reduce renal fibrosis in a mouse model of ischemia–reperfusion injury [23]. These reports suggest that PDGF-β/PDGF-R axis play important roles in the repair of damaged kidney. It is well known that imatinib has more inhibitory effect on PDGF-R than c-KIT or BCR-ABL [14]. Therefore, the renal impairment due to imatinib might be related, at least in part, to the inhibitory effects on PDGF-R by imatinib. It is also well known that nilotinib is one of the selective inhibitors for BCR-ABL. These factors might be associated with our findings that changes from imatinib to second generation TKIs could improve renal impairment with imatinib.

Recently, Vidal-Petiot E et al. have reported that imatinib inhibits tubular secretion of creatinine and this inhibition increases the level of sCrn independently of glomerular damage [24]. Imatinib exerts inhibitory effect on the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE) transporters 1- and 2-K on HEK293 in vitro [25, 26]. OCT2 exists in the basolateral membrane of the proximal tubule and MATE transporters exists in the apical membrane of the proximal tubule. These molecules have important roles in tubular selection of creatinine [27, 28]. Thus, there could be the possibilities that the blockage of creatinine tubular secretion by imatinib may increase serum creatinine (sCrn).

In conclusion, our study showed that long-term treatment with imatinib for CML induced the impairment of renal functions which had been improved with the changes from imatinib to second generation TKIs.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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