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ORIGINAL ARTICLE

Rapid decrease in eGFR with concomitant use of tyrosine kinase inhibitors and renin–aldosterone–angiotensin system inhibitors in patients with chronic myelogenous leukemia

Mariko Tsuda[1] · Akie Hirata[2] · Shoji Tokunaga[2] · Toru Masuda[1] · Shojiro Haji[1] · Daisaku Kimura[1] · Chinatsu Nojiri[2] · Yasuhiro Nakashima[1] · Motoaki Shiratsuchi[1,3] · Koji Kato[4] · Toshihiro Miyamoto[4] · Koichi Akashi[4] · Naoki Nakashima[2] · Yoshihiro Ogawa[1]

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Abstract

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML). However, TKI-related chronic renal toxicity has been reported, particularly in patients with hypertension. We assessed whether incidental use of specific types of antihypertensive drugs, including renin–aldosterone–angiotensin system inhibitors (RAASis), affects the change in estimated glomerular filtration rate (eGFR) during TKI treatment. We retrospectively analyzed all eGFR measurements during TKI treatment for 142 CML patients at Kyushu University Hospital, estimating the rate of eGFR change using a mixed-effects model. Overall, a significant interaction was found between the type of antihypertensive medication used and the yearly change in eGFR ($P < 0.01$), with RAASi users exhibiting the most rapid decrease in eGFR (−5.5%/year). The analysis by TKI used showed that the interaction was significant only in imatinib and bosutinib users ($P < 0.01$ and $P = 0.04$, respectively). The yearly rate of eGFR decrease was the most notable in RAASi users, at −5.7 (−6.6, −4.9) and −10.1 (−12.3, −7.9) for imatinib and bosutinib users, respectively. Our findings indicate that eGFR should be carefully monitored in patients taking these TKIs.

Keywords Imatinib · Bosutinib · Hypertension · Mixed effects model · RAASi

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML). Imatinib was the first TKI to be successfully used in clinical practice and provides not only progression-free and overall survival advantages, but also exhibits fewer adverse effects when compared with the previous standard therapy with cytarabine and interferon [1]. Second-generation TKIs, such as nilotinib, dasatinib, and bosutinib, have demonstrated efficacy and safety in patients resistant to or intolerant of imatinib [2–4], and they have more recently been used as initial therapies [5–7]. Ponatinib is a third-generation TKI that exhibits significant antileukemic activity against CML involving common ABL1 kinase domain mutations, including T315I [8, 9].

Although TKIs have relatively good safety profiles, adverse events, such as renal toxicity and cardiovascular events are often observed with long-term use [10, 11]. The previous reports have demonstrated that TKI-related chronic renal toxicity during long-term imatinib therapy is associated with a significant decrease in the estimated glomerular filtration rate (eGFR) [12–16]. In addition, hypertension, a well-known critical risk factor for the progression of chronic kidney disease (CKD) [17], has been shown to be the most common cardiovascular adverse event in TKI-treated

Mariko Tsuda and Akie Hirata contributed equally to this work.

✉ Yasuhiro Nakashima
nakashima.yasuhiro.717@m.kyushu-u.ac.jp

[1] Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

[2] Medical Information Center, Kyushu University Hospital, Fukuoka, Japan

[3] Department of Hematology, Iizuka Hospital, Iizuka, Japan

[4] Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

patients. The incidence of grade 3 hypertension during therapy with ponatinib, imatinib 400 mg per day, imatinib 800 mg per day, nilotinib, and dasatinib has been found to be 28%, 21%, 20%, 16%, and 5%, respectively [18].

However, some agents for treating hypertension can protect against the deterioration of renal function. For example, renin–aldosterone–angiotensin system inhibitors (RAASis) such as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors are recommended for hypertensive patients with proteinuria or CKD with microalbuminuria [19].

We hypothesized that RAASi use may prevent the decrease in eGFR caused by TKI in CML patients. The present study included 142 patients diagnosed with chronic-phase CML. All laboratory measurements of eGFR during treatment with imatinib, nilotinib, dasatinib, bosutinib, or ponatinib were retrospectively analyzed. The aim of this study was to estimate the rate of change in eGFR during use of each type of TKI according to the incidental use of various antihypertensive drugs. We also examined whether the annual rate of change in eGFR differed among RAASi users, non-RAASi users, and patients not on antihypertensive drugs.

Methods

Study patients

A flow diagram of the patients included in the analysis is shown in Fig. 1. The initial group of patients enrolled in this study included those who had been diagnosed with CML and prescribed a TKI between January 1, 2009 and December 31, 2020 at Kyushu University Hospital. Patients who had used more than one type of TKI were classified as independent cases. For each case, the change in eGFR between starting the different TKIs was monitored. To estimate the glomerular filtration rate, the estimation equation for Japanese patients with chronic kidney disease was applied [20]:

$$\begin{aligned}&\text{eGFR (mL/min/1.73 m}^2\text{)}\\&= 194 \times \text{Serum creatinine}^{-1.094}\\&\times \text{Age}^{-0.287}(\times 0.739,\ \text{if female}).\end{aligned}$$

From a total of 227 study cases, the following patients were excluded: those without any eGFR measurements ($n = 1$), those with serum creatinine (sCre) > 3 mg/dL at baseline ($n = 3$), those with eGFR < 30 mL/min/1.73 m^2 at baseline ($n = 7$), those diagnosed with CKD at baseline ($n = 6$), and those < 20 years old at baseline ($n = 16$).

Thus, a total of 203 cases treated with one of five types of TKI were categorized into three groups based on the use

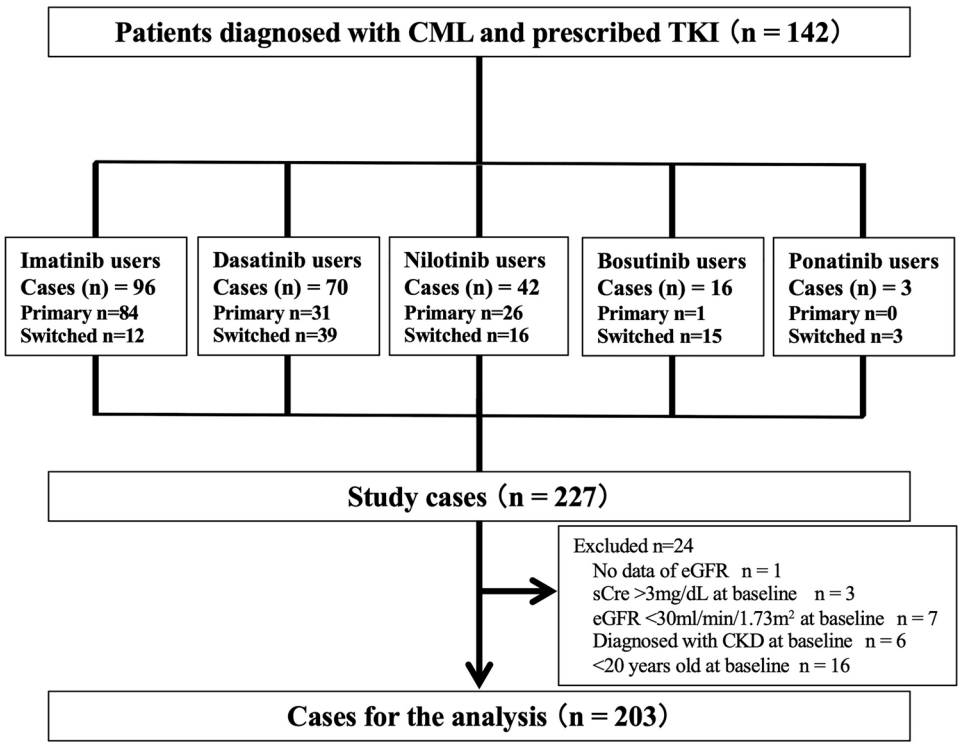

Fig. 1 Flow diagram of patients included in the analysis. The number of patients treated with each type of TKI was determined, including those who were first treated with a given TKI during the study period "Primary") and those who were treated with a TKI after treatment with another TKI ("Switched"). *CML* chronic myelogenous leukemia, *TKI* tyrosine kinase inhibitor, *eGFR* estimated glomerular filtration rate, *sCre* serum creatinine, *CKD* chronic kidney disease

of antihypertensive drugs: those treated with RAASis, those treated with antihypertensive drugs other than RAASis (e.g., calcium blockers, α-/β-blockers, and diuretics), and those who did not receive any antihypertensive agents. Informed consent was obtained by the opt-out method; information regarding the research, including the aims of use of specimens and the opportunity to opt out, was made public, and none of the recruited patients objected to the study. The study was approved by the ethics committee of Kyushu University Hospital (21007-00) and adhered to the principles of the Declaration of Helsinki.

Data collection

The data used in the present analysis were obtained from the electronic medical records (EMRs) of Kyushu University Hospital. The following data were extracted: diagnoses assigned with the International Classification of Disease, 10th edition (ICD-10) codes; date of diagnosis; prescription of antihypertensive drugs, including brand names and dates of prescription; laboratory test dates and results of eGFR measurements; and patient characteristics, including sex, birth year and month, body mass index, and smoking status. Diagnoses of CML and comorbidities such as diabetes and CKD were identified by the ICD-10 codes C92, N183/N184, and E14, respectively. A certain TKI case was defined as a patient using a TKI at any time during the treatment course. Patients who used more than two TKIs were included in each TKI group. Patients who were prescribed antihypertensive drugs during TKI treatment were counted as antihypertensive drug users.

Statistical analysis

We conducted the present observational study according to the STROBE criteria [21]. Characteristics of study cases at the start of TKI use were summarized as medians and ranges for continuous variables and numbers and percentages for categorical variables.

We first evaluated the statistical significance of the interaction between the type of antihypertensive drug used and the change in eGFR for all patients and those treated with each TKI. Second, we estimated the rate of change in eGFR (per year) separately for each group of antihypertensive drug with a mixed-effects model based on repeatedly measured eGFR values during the treatment period for each TKI group. Mixed-effects models can analyze repeated observations of the same subject, clustering repeated observations at the level of the subject. They can handle unequal intervals between observations, unequal numbers of observations per cluster, and randomly missing data [22]. The model fitted was as follows: let y_{ij} be the response variable (eGFR), measured on an individual patient i at a random time point t_j during the observational period: β_0 is the intercept; β_1 to β_5 are estimated coefficients; $D1$ and $D2$ represent a set of dummy variables for the type of antihypertensive drug indicating RAASis and non-RAASis, respectively; $t_j \times D1$ and $t_j \times D2$ are interaction terms between time and the type of antihypertensive drug; and e_{ij} is the error term. In this model, a statistically significant interaction means that the yearly change rate of eGFR was significantly different according to the type of antihypertensive drug;

$$y_{ij} = \beta_0 + \beta_1 t_j + \beta_2 D1 + \beta_3 D2 + \beta_4 t_j \times D1 + \beta_5 t_j \times D2 + e_{ij}.$$

The eGFR value was log-transformed to estimate the rate of change. We analyzed the data using the model with log(eGFR) as the dependent variable. A compound symmetry model was used as the covariance matrix. The likelihood ratio test was conducted to test the statistical significance of the coefficient for the explanatory variable. The explanatory variables in the univariate analysis were years from the start of TKI use to dates of eGFR measurement, a set of dummy variables indicating the use of antihypertensive drugs categorized into three groups, and interaction between years from the first TKI use to time of eGFR measurement and the type of antihypertensive drug. In the multivariate analysis, the following variables were further added in the model as covariates: log(eGFR) at the start of TKI, the presence of diabetes, habitual smoking, and use of diuretics. Because diabetes and habitual smoking are known risk factors for CKD [23], we used these variables as adjustment factors that could be obtained from the EMR. We adopted the presence of diuretics use as an adjustment factor, because Cortes et al. reported it as a risk factor for low eGFR in patients using imatinib or bosutinib [24].

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided P value of < 0.05 was considered statistically significant.

Results

A total of 203 cases were included in the analysis. Eighty-four of the cases received imatinib, 63 dasatinib, 37 nilotinib, 16 bosutinib, and only 3 received ponatinib (Table 1). The proportion of RAASi use was higher among cases treated with imatinib (27%) and bosutinib (44%) than other TKIs. In contrast, nearly half of the cases treated with dasatinib (43%) or nilotinib (46%) did not use any antihypertensive drugs. The ponatinib group did not contain any RAASi users. All groups were predominantly male. The median age of cases in the bosutinib group was higher than that of other TKI groups. The median eGFR at the start of imatinib and bosutinib administration tended to be lower (73.1 and 71.4 mL/min/1.73 m^2, respectively) than that of patients treated with

Table 1 Demographic and clinical characteristics of patients at the start of treatment with various TKIs

	Imatinib ($n=84$)	Dasatinib ($n=63$)	Nilotinib ($n=37$)	Bosutinib ($n=16$)	Ponatinib ($n=3$)
Use of antihypertensive drugs, *n* (%)					
RAASi	23 (27)	12 (19)	5 (13)	7 (44)	0
Non-RAASi	30 (36)	24 (38)	15 (41)	7 (44)	2 (67)
None	31 (37)	27 (43)	17 (46)	2 (13)	1 (33)
RAS only, *n* (%)	6 (7)	3 (5)	0	2 (13)	0
Ca blocker, *n* (%)	19 (23)	9 (14)	8 (22)	4 (25)	0
α/β Blocker, *n* (%)	13 (15)	7 (11)	2 (5)	3 (19)	0
Number of antihypertensive drugs, *n* (%)					
1	28 (33)	22 (35)	12 (32)	8 (50)	0
2	12 (14)	7 (11)	6 (16)	2 (13)	2 (67)
≥3	13 (15)	7 (11)	2 (5)	4 (25)	0
eGFR (mL/min/1.73 m^2), median (range)	73.1 (34.4–112.2)	82.2 (38.3–123.9)	82.3 (46.3–118.0)	71.4 (50.5–97.3)	84.2 (63.8–89.1)
sCre, median (range)	0.83 (0.50–1.62)	0.78 (0.44–1.46)	0.74 (0.40–1.30)	0.87 (0.76–1.26)	0.74 (0.73–0.82)
Age (years), median (range)	54 (21–90)	49 (22–75)	53 (22–85)	60 (30–73)	50 (39–53)
Sex, *n* (%)					
Male	54 (64)	42 (67)	21 (57)	16 (100)	2 (67)
Female	30 (36)	21 (33)	16 (43)	0	1 (33)
Presence of diabetes (yes), *n* (%)	19 (23)	24 (38)	13 (35)	6 (38)	1 (33)
Current/past smoking (yes), *n* (%)	25 (30)	15 (24)	9 (24)	9 (56)	1 (33)
Use of diuretics (yes), *n* (%)	39 (46)	32 (51)	14 (38)	10 (63)	2 (67)

TKI tyrosine kinase inhibitor, *RAASi* renin–aldosterone–angiotensin system inhibitor, *eGFR* estimated glomerular filtration rate, *sCre* serum creatinine

other TKIs. The proportion of cases with diabetes was lower among those treated with imatinib (23%) when compared with those treated with other TKIs. The bosutinib group included more smokers (56%) than the other groups. The use of diuretics was more common among cases treated with bosutinib (63%) and ponatinib (67%).

Figure 2 shows the eGFR for each TKI course over time after the first administration. These plots were used to choose the appropriate model for the statistical analysis. Yearly changes in eGFR and the 95% confidence intervals (CIs) (%) for each antihypertensive drug group estimated from the statistical model are shown in Fig. 3, according to the type of TKI. Because none of the ponatinib users were prescribed RAASis, the ponatinib group could not be analyzed using the mixed-effects model. Ponatinib-user data were therefore used only in the modeling of all cases. For the users of nilotinib and bosutinib, in calculating the yearly change rate of eGFR according to the antihypertensive drug group, multivariable adjustment could not be applied due to the insufficient number of patients. Therefore, the interaction between the type of antihypertensive drug and changes in eGFR as well as the yearly change rate of eGFR were tested without adjustment for covariates (Fig. 3).

Overall, a significant interaction between the type of antihypertensive medication used and yearly change in eGFR was observed ($P<0.01$). Point estimates (95% CIs) of the yearly change (%) in eGFR were −5.5 (−6.2, −4.8), −2.8 (−3.2, −2.5), and −3.0 (−3.2, −2.8) for the RAASi, non-RAASi, and no-drug groups, respectively, suggesting that the decrease in eGFR in RAASi users was more rapid than in users of other antihypertensive drugs (*P* for interaction, <0.01). In analyses specific to imatinib and bosutinib users, significant interactions were also found between the type of antihypertensive medication used and the annual rate of change in eGFR ($P<0.01$ and $P=0.04$, respectively). The yearly rate of decrease in eGFR (95% CI) was more notable in the RAASi group for imatinib users (−5.7 [−6.6, −4.9]) and bosutinib users (−10.1 [−12.3, −7.9]), respectively, when compared with the non-RAASi and no-antihypertensive drug groups. However, among cases treated with dasatinib, no statistically significant interaction was found between the rate of change in eGFR and type of antihypertensive drug used ($P=0.14$). In the nilotinib group, a significant interaction between the type of antihypertensive medication used and the yearly rate of change in eGFR was observed ($P<0.01$), with the decrease in eGFR being slower in cases not using any antihypertensive drug. The yearly rate of decrease in eGFR (95% CI) was −3.1 (−4.3, −1.8), −2.4 (−3.0, −1.9), and −1.7 (−2.1, −1.4) in the RAASi, non-RAASi, and no-antihypertensive drugs groups, respectively. In an additional analysis adjusting for the value of log(eGFR) at the start of nilotinib and bosutinib in the

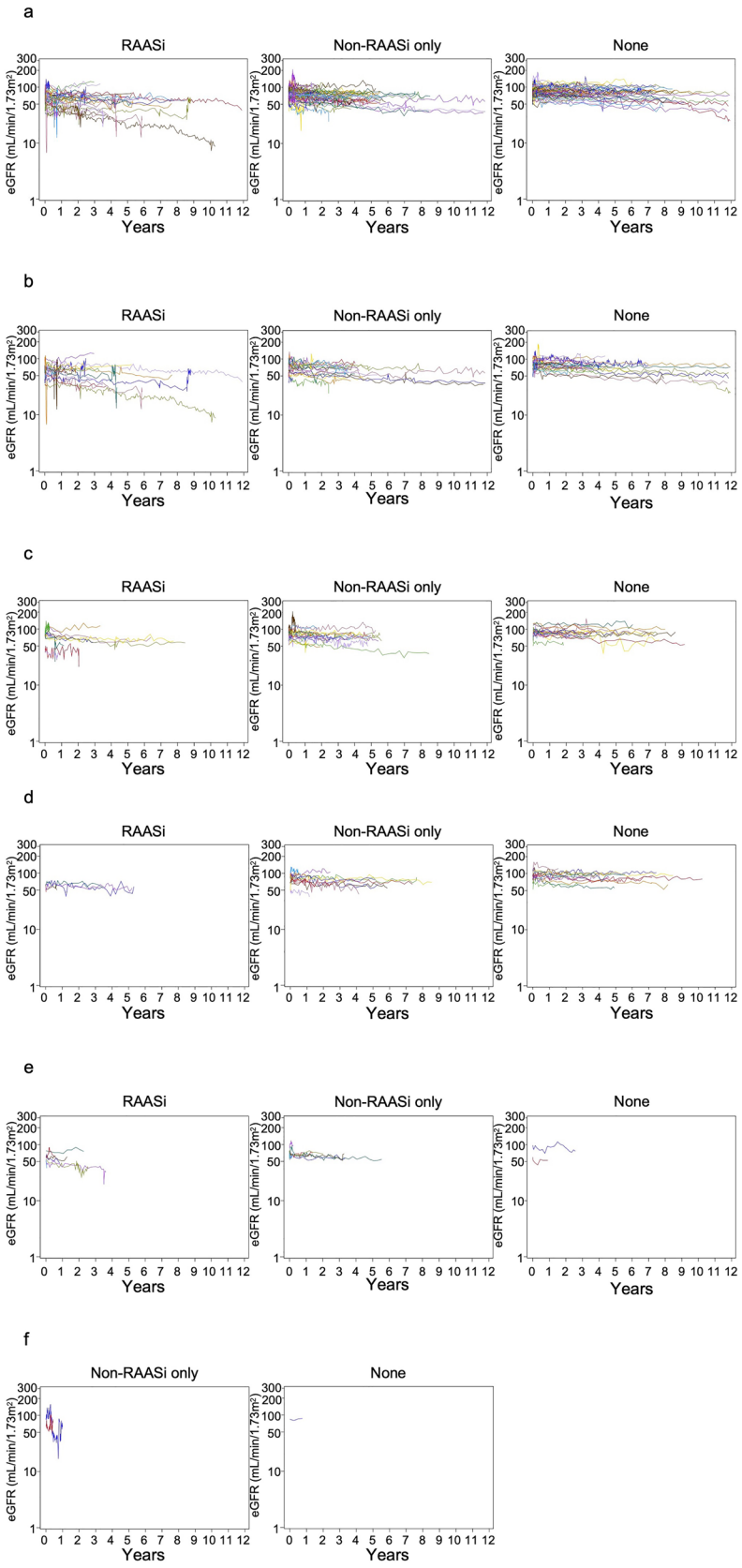

Fig. 2 Change in eGFR during treatment with various TKIs. Changes in eGFR during treatment with specific TKIs are shown as line plots according to the use of antihypertensive drugs for **a** all patients, **b** patients treated with imatinib, **c** patients treated with dasatinib, **d** patients treated with nilotinib, **e** patients treated with bosutinib, and **f** patients treated with ponatinib. Each colored line reflects all eGFR measurements over time for one patient taking one particular TKI. *TKI* tyrosine kinase inhibitor, *eGFR* estimated glomerular filtration rate, *RAASi* renin–aldosterone–angiotensin system inhibitor

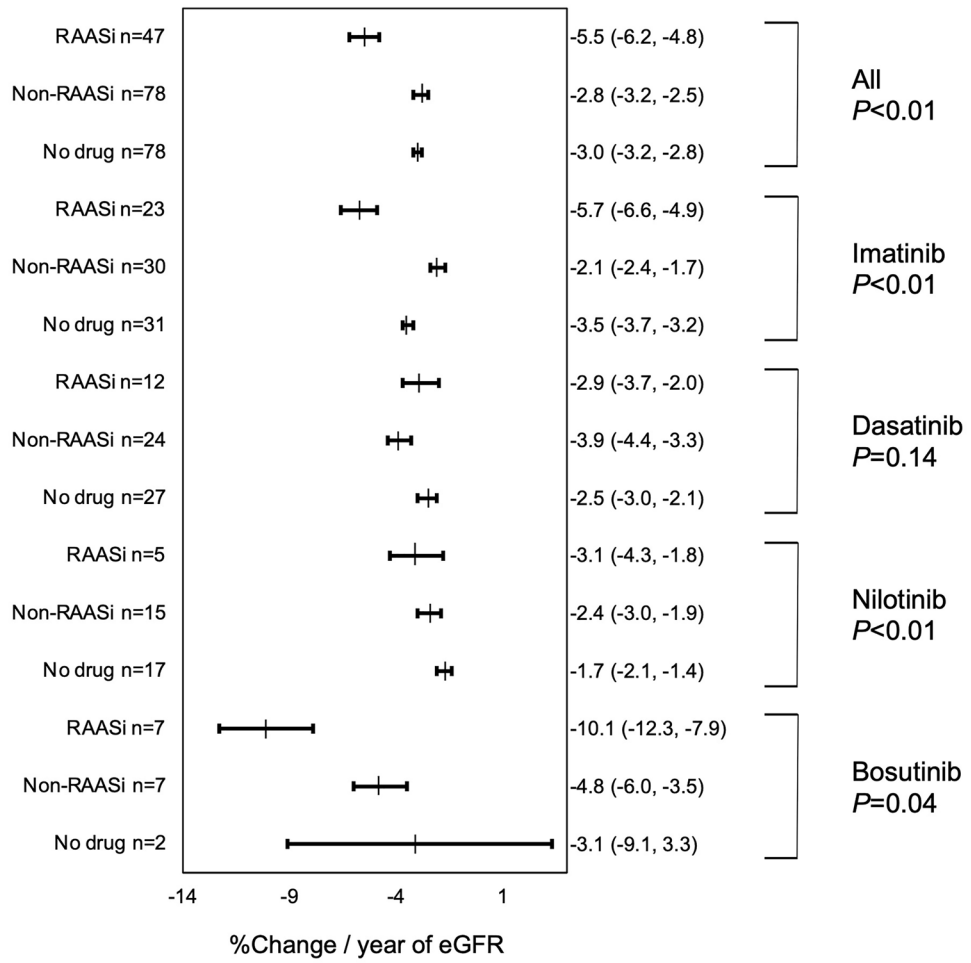

Fig. 3 Annual rate of change in eGFR (%) and 95% CIs estimated using a mixed-effects model. Estimated changes in eGFR (%) per year and 95% CIs (%) are shown for all patients, patients treated with imatinib, patients treated with dasatinib, patients treated with nilotinib, and patients treated with bosutinib, and are plotted as crossbars and error bars according to the use of three types of antihypertensive drugs. Point estimates and 95% CIs were estimated using a mixed-effects model; multivariate adjustment for log(eGFR) at the start of TKI treatment, the presence of diabetes, habitual smoking, and use of diuretics was employed in the analyses of all patients and patients treated with imatinib or dasatinib. *P* for interaction between the rate of change rate in eGFR and the type of antihypertensive drug used are shown for each category of TKI. *TKI* tyrosine kinase inhibitor, *eGFR* estimated glomerular filtration rate, *CI* confidence interval, *RAASi* renin–aldosterone–angiotensin system inhibitor

mixed-effects model, the interactions between the type of antihypertensive drug and yearly changes in eGFR were also statistically significant for nilotinib users ($P < 0.01$) and marginally significant for bosutinib users ($P = 0.05$) (data not shown).

Discussion

The present findings show that a significant interaction between the type of antihypertensive medication used and the yearly change in eGFR was particularly evident among imatinib and bosutinib users, and the decrease in eGFR was more rapid in the RAASi group than in other groups. In contrast, RAASi use did not affect the rate of decrease in eGFR in CML patients treated with dasatinib or nilotinib.

Several studies have examined renal function in patients undergoing long-term treatment with imatinib [12–16]. In some of those studies, imatinib was more likely to cause a decline in eGFR than nilotinib or dasatinib [14, 16]. Another study reported that long-term bosutinib treatment is associated with an apparent decline in renal function, with a median change in eGFR from baseline to 48 months of -15.62 mL/min/1.73 m^2 with bosutinib and -17.69 mL/min/1.73 m^2 with imatinib [24]. This report suggested that baseline factors associated with the development of eGFR < 45 mL/min/1.73 m^2 include older age, proteinuria, lower baseline eGFR, and previous hypertension. That report also identified time-dependent prognostic factors associated with eGFR < 45 mL/min/1.73 m^2 as use of antihypertensive agents or loop diuretics, grade 3/4 vomiting, and congestive heart failure. However, to our knowledge, no study has examined the effect of incidental antihypertensive drug use on the association between TKIs and the deterioration of renal function. The present study is the first to focus on the effect of a specific type of antihypertensive medication on the change in eGFR among TKI users.

The mechanism underlying the decline in eGFR in patients treated with the combination of imatinib or bosutinib and RAASis remains unknown. One possibility is that certain clinical backgrounds may be associated with both the choice of RAASi and the decline in eGFR. The results of multivariate analyses adjusted for the presence of diabetes, current/past smoking, and eGFR at the start of TKI

treatment differed from our original hypothesis. Thus, other factors that confound the association between RAASi use and rapid decline in eGFR may exist. Clinicians should further be aware that dasatinib can cause side effects of cardiovascular events, and nilotinib, moreover, has been shown to be related to the exacerbation of diabetes [25, 26]. As there is an association between reduced eGFR and the risk of cardiovascular events [27], clinicians might choose imatinib or bosutinib with a RAASi for patients who are at high risk of CKD.

Another possibility is that dehydration caused by imatinib or bosutinib may accelerate the decrease in eGFR in RAASi users. It is reported that 24.2% of imatinib users suffer from gastrointestinal adverse events [28]. Moreover, bosutinib can cause diarrhea, vomiting, nausea, and increased risk of infection [4], each of which has the potential to result in a hypovolemic state that could lead to renal dysfunction. In addition, RAASis can cause acute renal insufficiency, particularly in older patients, with consequent dehydration related to poor water intake, vomiting, diarrhea, and excessive sweating, especially with concomitant use of diuretics [19, 29]. Although we adjusted for the use of diuretics among imatinib users in the multivariate analysis, in this retrospective study protocol, we did not have information regarding other clinical states related to dehydration, such as gastrointestinal symptoms, infection, and congestive heart failure.

The present study has some limitations. First is the retrospective data collection. Available information regarding clinical background related to the change in eGFR and the choice of TKI and/or antihypertensive drugs was limited in the present analysis. In addition, we did not have information regarding all types of clinical signs indicative of deteriorated renal function. Such clinical information, which could only be effectively collected using a study protocol designed in advance, might confound the associations observed in the present analysis. Thus, the rapid decrease in eGFR among RAASi users found in the present study should be examined further to determine whether RAASi use is sufficient to drive renal dysfunction in patients treated with TKIs when considering other potential factors associated with the choice of RAASi. Second, misclassification of patient comorbidities was a concern due to limitations in the information available in the EMRs. As the data included in the present analysis were all based on the EMRs of our hospital, we might have overlooked the presence of diseases such as diabetes that may have been treated at other clinics. Moreover, we could not precisely determine whether TKIs started in our hospital were first-line treatments. Xin et al. reported that nilotinib and dasatinib did not have any impact on decreasing eGFR as a first-line therapy, but they had mild adverse impacts as second- or third-line therapies [15]. In the present study, although almost half of the cases treated with dasatinib were identified as first-line users, data regarding the history of treatment with other TKIs at other hospitals were not fully available. Thus, it remains unclear whether the present findings in patients receiving dasatinib were related to first-line use of this drug. To make the best use of data extracted from EMRs, which carry the significant advantage of providing a large number of eGFR values measured over multiple years, future studies addressing additional clinical information unavailable in the EMR may be needed. Finally, the small number of subjects precluded a sufficient evaluation of the interaction between the type of antihypertensive drug used and the rate of change in eGFR among patients taking ponatinib. For nilotinib and bosutinib users, multivariate adjustment was not possible due to an insufficient number of cases. However, the significantly more rapid decease in eGFR among RAASi users treated with bosutinib is noteworthy and should be examined further in a study including more patients and taking into account clinical backgrounds possibly related to the choice of RAASi.

Conclusion

Compared with CML patients treated with other TKIs, a significantly more rapid decrease in eGFR was found among imatinib or bosutinib users concurrently treated with a RAASi. Thus, eGFR should be carefully monitored in CML patients treated with these specific TKIs and simultaneously receiving a RAASi.

Declarations

Conflict of interest Mariko Tsuda received honoraria/lecture fees from Otsuka related to this study. Sojiro Haji received honoraria/lecture fees from Kyowa Kirin unrelated to this study. Yasuhiro Nakashima received research grants from the Japanese Society of Hematology, and research grant supports from Chugai, Kyowa Kirin, Daiichi Sankyo and SRL, honoraria/lecture fees from Otsuka related to this study, and Chugai, Kyowa Kirin, Ono and Sanofi, unrelated to this study. Motoaki Shiratsuchi received research grant supports from Chugai, Kyowa Kirin, Daiichi Sankyo, MSD and SRL, honoraria/lecture fees from Otsuka related to this study, and Chugai, Kyowa Kirin, Ono and Sanofi, unrelated to this study. Koji Kato received research grant supports from Chugai, Takeda, Kyowa Kirin, AbbVie, Novartis, Eisai, Janssen, Celgene, Ono and Daiichi Sankyo, honoraria/lecture fees from Kyowa Kirin, Novartis, Takeda and Chugai, unrelated to this study. Toshihiro Miyamoto received honoraria/lecture fees from Takeda, Otsuka, MSD, Kyowa Kirin, Janssen, Astellas and AbbVie. Koichi Akashi received research grant supports from Otsuka, Nippon Shinyaku, Taiho, Asahi Kasei, Chugai, Takeda, Kyowa Kirin, AbbVie, Sumitomo Dainippon, Astellas, Bristol Myers Squibb and Eisai, honoraria/lecture fees from AbbVie, Eisai, Ono, Kyowa Kirin, Chugai, Pfizer, Bristol Myers Squibb and Janssen, unrelated to this study. Naoki Nakashima received research grant supports from Pfizer unrelated to this study. Yoshihiro Ogawa received research grant supports from Kyowa Kirin, Taisho,

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