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ORIGINAL ARTICLE

Assessment of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase receiving tyrosine kinase inhibitors

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Abstract

We aimed to evaluate the incidence of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase (CML-CP) receiving tyrosine kinase inhibitors (TKIs) and to identify the associated factors. Data for CML-CP patients with normal estimated glomerular filtration rate (eGFR) at baseline and receiving TKI therapy ≥ 3 months were retrospectively reviewed. The CRAE (chronic renal adverse event, defined as a 30% eGFR reduction from baseline or eGFR < 60 ml/min/1.73 m^2 ≥ 90 days whichever occurred first)-free survival rates at 3 years in the imatinib cohort ($n = 360$) were significantly lower than those in the nilotinib cohort ($n = 100$) (55% versus 77%, $P = 0.001$) as a first-line TKI therapy. In multivariate analyses, imatinib, male sex, increasing age, and previous non-TKI treatment were associated with poor CRAE-free survival. In newly diagnosed patients who received imatinib treatment ($n = 40$), 24-h urine protein levels significantly increased after 6 months, and urinary β_2-microglobulin values significantly increased compared to those in the nilotinib cohort ($n = 15$) at 36 months ($P = 0.042$) and 42 months ($P = 0.039$). There was no significant difference in CRAE-free survival rates at 3 years between the nilotinib ($n = 65$) and dasatinib ($n = 74$) cohorts (67% versus 83%, $P = 0.832$) as second- or third-line TKI therapies. In multivariate analyses, previous non-TKI treatment was associated with poor CRAE-free survival. We concluded that imatinib was significantly correlated to chronic renal injury, possibly associated with glomerulus and renal tubular injury, compared with nilotinib as a first-line TKI therapy in CML-CP patients. However, nilotinib and dasatinib had similar mild adverse impacts on renal function as second- or third-line therapies.

Keywords Chronic myeloid leukemia · Tyrosine kinase inhibitors · Chronic renal injury

Introduction

Patients with chronic myeloid leukemia (CML) in the chronic phase (CP) have a normal lifespan when treated with tyrosine kinaseinhibitors (TKIs). However, TKI-related adverse events have attracted much attention because they may impact organ function, adherence, and satisfaction with TKI therapy and result in poor treatment outcomes. TKI-related chronic renal toxicity has been reported in limited studies [1–5]. Previous studies showed that long-term imatinib therapy may cause a significant decrease in the estimated glomerular filtration rate (eGFR) [1–4] and is more likely to cause chronic renal injury than nilotinib and dasatinib; moreover, switching imatinib to nilotinib or dasatinib could improve renal function [2–4]. In these studies, chronic kidney disease (CKD) was one of the clinical endpoints and was assessed in patients regardless of the eGFR values at baseline.

It is well known that measuring the creatinine concentration is not a sensitive test for determining renal function; GFR, estimated with the Modification of Diet in Renal Disease equation, is considered to be a more accurate assessment index. Currently, it has been widely accepted that a smaller reduction (such as a 30% decline) from baseline eGFR values may capture a much higher proportion of subsequent mortality-related CKD progression across cohorts with both lower and higher baseline eGFR values, providing an

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alternative and more accurate kidney endpoint for clinical trials, observational studies and clinical practice, with greater power over shorter periods of follow-up [6].

Currently, several TKIs have been approved as first-line therapies in many countries [7]. However, imatinib and nilotinib have been approved as front-line TKI therapies in patients with CML in China, while dasatinib has been approved as a second- or third-line option. To better understand the renal safety profiles of TKIs and to identify factors associated with TKI-related chronic renal injury, we retrospectively analyzed data from 564 CML-CP patients with normal renal functions at baseline during imatinib, nilotinib, or dasatinib treatment as first-, second- or third-line therapies.

Materials and methods

Patients

From March 2001 to August 2017, the medical records of 595 consecutive adult CML-CP patients who received imatinib (Glivec®), nilotinib (Tasigna®), or dasatinib (Sprycel®) as first-, second-, or third-line TKI therapies for ≥ 3 months at Peking University People's Hospital were retrospectively reviewed. Patients with abnormal renal function (eGFR < 60 ml/min/1.73 m^2) at baseline or whose laboratory examinations were irregularly monitored were excluded in this study. Information regarding kidney-related comorbidities, medical history, concomitant medications, and clinical events that might be responsible for renal function change was also collected. The Ethics Committee of the Peking University People's Hospital approved this study, and all patients signed informed consent forms.

Detections and monitoring

Routine laboratory examinations, including complete blood counts, and a complete metabolic profile, including serum creatinine, were performed at baseline and monitored every 1 to 2 weeks during the first 3 months and every 3–6 months thereafter. From June 2011 to December 2013, chronic renal impairment-related indexes, including glomerular function, as assessed by 24-h urine protein levels and the urinary albumin-creatinine ratio, and renal tubular function, as assessed by urine osmolality and urinary β_2-microglobulin levels, were monitored in newly diagnosed (interval from diagnosis of CML to starting TKI therapy < 6 months) CML-CP patients from the baseline, every 3 months in the first year, and every 6 months thereafter. Hematologic, cytogenetic, and molecular responses were monitored as previously described [8]. In this study, we focused on renal function changes during TKI therapy.

Definitions

First-line TKI therapy was defined as the first TKI option the patient received. Second- or third-line TKI therapies were defined as those that a patient switched to after a first or second TKI option because of intolerance or resistance. If a patient received a first-line TKI therapy and switched to a second- or third-line TKI therapy for any cause except for disease progression to the accelerated phase (AP) or blast phase (BP), kidney-related data during the first, second, or third TKI therapies was collected and analyzed. Patients were followed from the start of TKI therapy to the end of the study evaluation period in November 2017 or to the last visit (in cases who died or were lost to follow-up). Patients were removed from the study when they switched to another treatment or following progression into the AP or BP.

The primary endpoint was the onset of a chronic renal adverse event (CRAE) in CML-CP patients. The secondary endpoints included the onset of CKD, changes in eGFR and serum creatinine values, and the changes in the 24-h urine protein, urinary albumin-creatinine ratio, urine osmolality, and urinary β_2-microglobulin values. CRAE was defined as a 30% reduction in eGFR values from the baseline that persisted ≥ 90 days or the onset of CKD, whichever occurred first. CKD was defined as an eGFR < 60 ml/min/1.73 m^2 that persisted for ≥ 90 days. The time point at which eGFR < 60 ml/min/1.73 m^2 or there was a reduction in eGFR ≥ 30% from the baseline after 3 months (included 3 months) was regarded as the time when chronic renal injury occurred. CRAE- or CKD-free survival was used to evaluate the onset of chronic renal injury, which was defined as the time between TKI treatment initiation and the onset of CRAE or CKD. Changes in the 24-h urine protein levels and the urinary albumin-creatinine ratio were used to identify renal injury to the glomerulus, and changes in the urine osmolality and urinary β_2-microglobulin values were used to identify renal injury to the renal tubule.

Statistical analysis

Categorical variables were reported as percentages and counts. Continuous variables were reported as medians and ranges. The Kruskal-Wallis test and the chi-squared test were used to evaluate differences between the cohorts receiving different TKIs. Patients' characteristics [age, sex, kidney-related comorbidity(ies) (such as hypertension, diabetes, coronary artery disease, and chronic renal failure), previous non-TKI treatment (such as hydroxyurea, interferon, and chemotherapy), interval from diagnosis of CML to starting current TKI therapy, current TKI used, and concomitant medication(s)] were analyzed to identify factors associated with the onset of chronic renal injury during TKI therapy. Statistically significant differences in the levels of eGFR, serum creatinine,

24-h urine protein, urinary albumin-creatinine ratio, urine osmolality, and urinary β_2-microglobulin were calculated with a paired samples Student's *t* test between the values at baseline and at each time point. The Kaplan-Meier method was used to assess statistical significance in the time-to-event analyses. Univariate and multivariate analyses were performed to determine whether any of the selected factors were predictive of CRAE- and CKD-free survival. Factors at a level of $P < 0.20$ were included in a Cox regression model. Factors with an effect significant at the level of $P \leq 0.05$ were interpreted as being independently predictive of the outcomes. All statistical analyses were performed with SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

Data for 595 consecutive CML-CP patients were reviewed. A total of 31 patients were excluded because they had eGFR values < 60 ml/min/1.73 m^2 at baseline and seven patients were removed due to progression to AP or BP. A total of 564 patients were included in this study (Fig. 1). Because 27 patients switched from imatinib to nilotinib ($n = 8$) or dasatinib ($n = 19$) and eight patients switched from nilotinib to dasatinib due to TKI-resistance, 599 cases with available baseline data for creatinine and eGFR, including imatinib ($n = 360$), nilotinib ($n = 165$), and dasatinib ($n = 74$), were analyzed. A total of 460 (77%) patients received first-line TKI therapies; 113 (19%) received second-line therapies, and 26 (4%) received third-line therapies.

Patients receiving first-line TKI therapies

Patient characteristics

A total of 460 patients received imatinib ($n = 360$) or nilotinib ($n = 100$) as first-line TKI therapies. Of these, 286 (62%) patients were male. The median age was 39 years (range of 18–87 years). A total of 75 patients (16%) had kidney-related comorbidity(ies). A total of 118 patients (26%) received hydroxyurea, interferon, or chemotherapy before the initiation of TKI therapy. A total of 92 patients (20%) took concomitant medication(s), such as antihypertensives and antidiabetics, during TKI therapy. The median serum creatinine value was 69 μmol/L (range of 28–107 μmol/L), and the median eGFR value was 94 ml/min/1.73 m^2 (range of 60–288 ml/min/1.73 m^2) at baseline. There were certain significant differences between the two cohorts, including more patients who received previous non-TKI treatment ($P = 0.012$) and having a longer TKI therapy duration ($P < 0.001$) in the imatinib cohort, and more patients receiving concomitant medication(s) ($P = 0.048$) and having a higher eGFR level ($P = 0.031$) at baseline in the nilotinib cohort (Table 1). With a median follow-up of 36 months (range of 3–

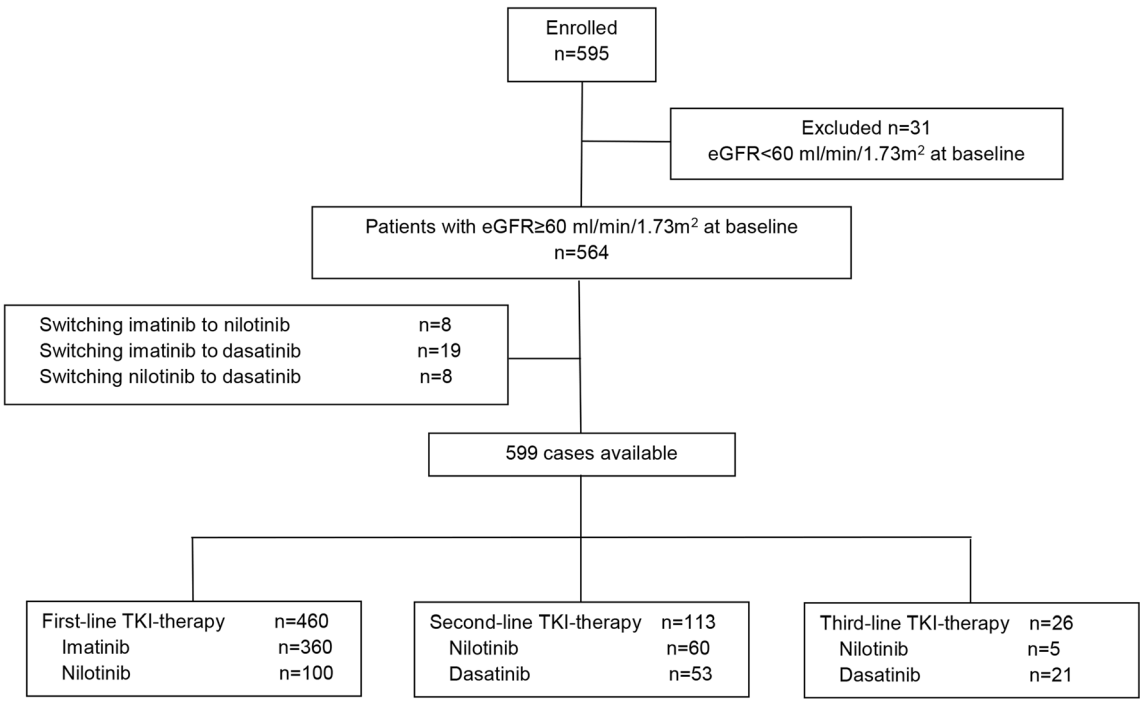

Fig. 1 Outline of patients in the study. TKI, tyrosine kinase inhibitor; eGFR, estimated glomerular filtration rate

Table 1 Clinical characteristics of the patients receiving first-line TKI therapies

Characteristics	Imatinib ($n = 360$)	Nilotinib (n = 100)	P
Male, no. (%)	225 (62.5)	61 (61.0)	0.784
Age, median (range), year	40 (18–87)	37 (18–80)	0.102
The starting dose of TKI, mg/d [No. (%)]	400 [360(100.0)]	800 [8 (8.0)]/600 [92 (92.0)]	
WBC, median (range), $\times 10^9$/L	15.2 (1.5–619.6)	15.6 (1.7–433.5)	0.752
Hemoglobin, median (range), g/L	123 (63–258)	114 (67–357)	0.001
Platelets, median (range), $\times 10^9$/L	355 (38–2227)	436 (9–2954)	0.011
PB basophils, median (range), %	4 (0–19)	7 (0–19)	< 0.001
PB blasts, median (range), %	0 (0–14)	0 (0–14)	0.001
BM basophils, median (range), %	2 (0–19)	3 (0–19)	< 0.001
BM blasts, median (range), %	2 (0–14)	2 (0–14)	0.324
Baseline creatinine, median (range), μmol/L	70.0 (28.0–107.0)	67.0 (38.0–98.0)	0.076
Baseline estimated GFR, median (range), ml/min/1.73 m^2	92.2 (60.0–287.6)	102.8 (62.0–219.4)	0.031
Comorbidity(ies)[a], no. (%)	65 (18.1)	10 (10.0)	0.054
Concomitant medication(s)[b], no. (%)	66 (18.3)	26 (26.0)	0.048
Previous non-TKI treatment, no. (%)	102 (28.3)	16 (16.0)	0.012
TKI-dose reduction, no. (%)	49 (13.6)	25(25.0)	0.006
TKI-dose at the end of follow-up, mg/d [no. (%)]	400 [311(86.4)]/300 [42(11.7)]/200 [7(1.9)]	800 [5 (5.0)]/600 [70 (70.0)]/400 [21 (21.0)]/300 [4 (4.0)]	
Interval from diagnosis to starting TKI therapy, median (range), month	1 (0–184)	1 (0–42)	0.150
Follow-up, median (range), month	42 (3–198)	23 (3–78)	< 0.001

Abbreviations: *TKI* tyrosine kinase inhibitor, *WBC* white blood cell, *PB* peripheral blood, *BM* bone marrow, *GFR* glomerular filtration rate

[a] Comorbidities included hypertension, diabetes, coronary artery disease, chronic renal failure, and hyperuricemia

[b] Concomitant medications included antihypertensive, antidiabetic, levothyroxine, and other consistently used drugs

198 months), 382 (83%) patients achieved complete cytogenetic response (CCyR) at a median time of 3 months (range of 1–72 months); 302 (66%) patients achieved major molecular response (MMR) at a median time of 9 months (range of 1–150 months); and 166 (36%) patients achieved deep molecular response (MR4.5) at a median time of 21 months (range of 3–150 months). None of the patients developed cardiovascular events during the follow-up period.

Changes in eGFR and serum creatinine values

With a median follow-up of 42 months (range of 3–198 months) in the imatinib cohort, the mean eGFR value significantly declined over time. However, with a median follow-up of 24 months (range of 3–78 months) in the nilotinib cohort, the mean eGFR value remained stable during the first 3 years and significantly declined after 42 months (Fig. 2a). However, the changes in creatinine values during the same period showed an opposite trend to that for eGFR levels in the two cohorts (Fig. 2b).

The onset of CRAE and CKD

In the imatinib cohort, 159 patients (44%) developed CRAE and 82 (23%) developed CKD, both at a median time of 12 months (range of 3–138 months). In the nilotinib cohort, 20 patients (20%) developed CRAE at a median time of 21 months (range of 3–72 months), and eight patients (8%) developed CKD at a median time of 6 months (range of 3–72 months). The probability of CRAE-free survival in the imatinib cohort was significantly lower than that in the nilotinib cohort as a whole ($P = 0.001$: at 1 year, 74% vs. 93%; at 2 years, 66% vs. 83%; at 3 years, 55% vs. 77%; at 4 years, 51% vs. 77%; at 5 years, 47% vs. 71%; and at 6 years, 44% vs. 43%). The same result happened in the probabilities of CKD-free survival ($P = 0.021$: at 1 year, 87% vs. 95%; at 2 years, 84% vs. 92%; at 3 years, 78% vs. 92%; at 4 years, 77% vs. 92%; at 5 years, 74% vs. 92%; and at 6 years, 72% vs. 86%) (Table 2; Fig. 3a, b).

In addition, there were no differences in the probabilities of CRAE-free survival ($P = 0.223$) and CKD-free survival ($P = 0.415$) at 3 years between the two subgroups

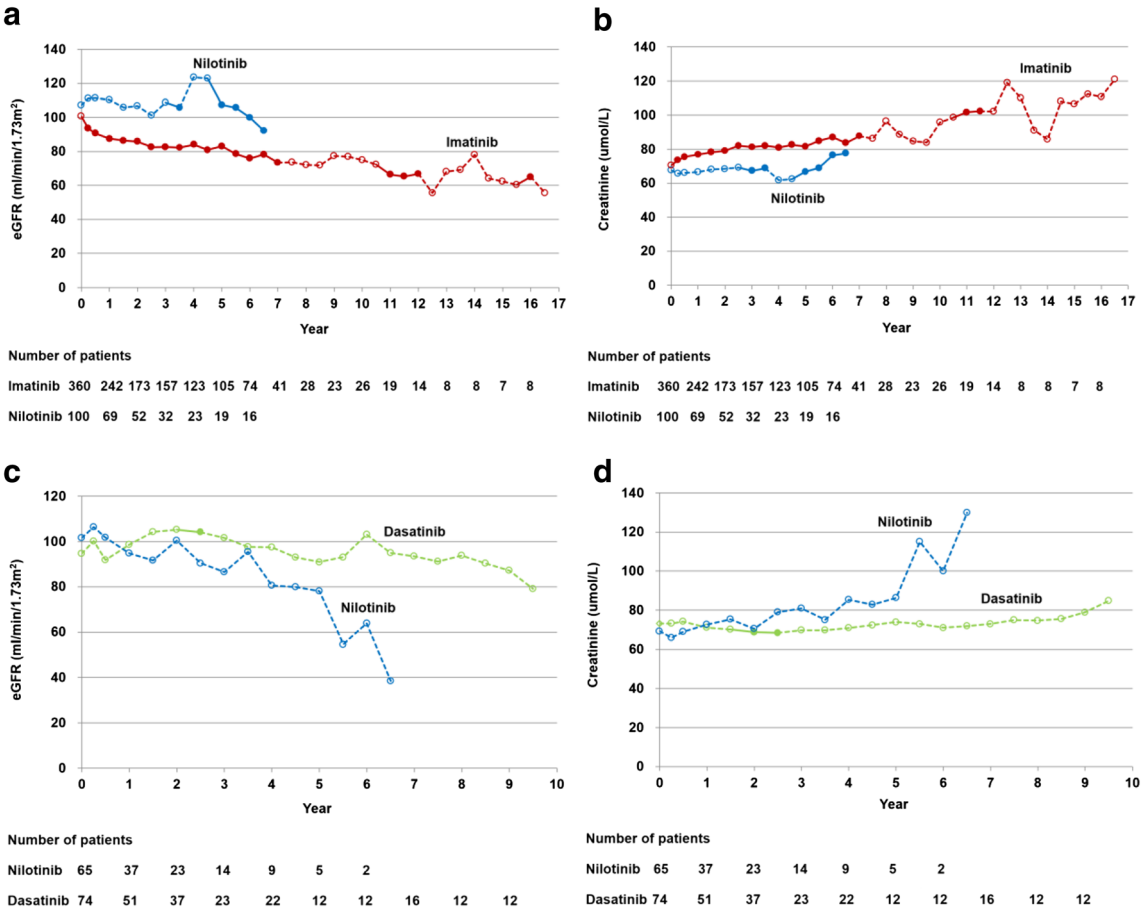

Fig. 2 Changes in eGFR and creatinine levels in patients receiving first-line (**a**–**b**) and second- or third-line TKI therapies (**c**–**d**). Statistically significant differences were calculated with a paired samples Student's *t* test between the baseline and each time point. Solid line and dot indicate $P < 0.05$. Dotted line and circle indicate $P > 0.05$

receiving nilotinib at initial doses of 600 mg/d and 800 mg/d.

Factors associated with CRAE and CKD

Patient characteristics, including age, sex, kidney-related comorbidity(ies), prior non-TKI treatment, interval from diagnosis of CML to starting TKI therapy, type of TKI therapy, and concomitant medication(s), were analyzed to identify factors associated with the onset of chronic renal injury. Multivariate analyses showed that imatinib rather than nilotinib was associated with a poor CRAE-free survival rate. In addition, male sex, increasing age, previous non-TKI treatment, and a longer interval from diagnosis of CML to starting TKI therapy were significantly associated with poor CRAE-free survival and/or CKD-free survival rates (Table 3).

According to the four risk factors associated with CRAE-free survival, including imatinib use, male sex, age ≥ 50 years, and previous non-TKI treatment, 460 patients were divided into three groups: low-risk (≤ 1 factor, $n = 145$), intermediate-risk (2 factors, $n = 198$), and high-risk (≥ 3 factors, $n = 117$). There were significant differences in CRAE-free survival at 3 years (low-risk: 82%, 95% CI 75–89%; intermediate-risk: 64%, 95% CI 57–72%; high-risk 46%, 95% CI 36–56%; $P < 0.001$) among the three groups (Fig. 3c).

Indexes associated with glomerular and renal tubular impairment

A total of 55 newly diagnosed CML-CP patients with normal renal function who received front-line imatinib ($n = 40$) or nilotinib ($n = 15$) therapy underwent regular monitoring of glomerular and renal tubular function from the baseline. With a median follow-up of 66 months (range of 42–66 months), 24-h urine protein levels significantly increased at several time points after 6 months compared with the baseline in the imatinib cohort, including those in 28 patients (70%) more than normal range (< 0.15 g/day) and those in 15 patients (38%) up to macroalbuminuria (≥ 0.3 g/day). However, in the nilotinib cohort, there was no significant difference on the change in 24-h urine protein levels compared with the baseline during the follow-up period despite the values in seven patients (47%) exceeding the normal range and those in two patients (13%) up to macroalbuminuria,

Table 2 Univariate analyses for CRAE-free survival and CKD-free survival rates at 3 years in patients receiving first-line TKI therapies

	CRAE-free survival		CKD-free survival	
	%	*P*	%	*P*
Sex		0.020		< 0.001
Male	57.1		74.4	
Female	65.2		92.0	
Age, year		0.002		< 0.001
< 30	65.6		92.8	
30–40	65.6		86.3	
40–50	66.6		83.7	
50–60	39.0		63.4	
≥ 60	36.6		50.0	
TKI		0.001		0.021
Nilotinib	76.8		91.7	
Imatinib	55.2		78.1	
Previous non-TKI treatment		< 0.001		0.001
Yes	50.6		69.4	
No	63.3		85.1	
Comorbidity(ies)		0.006		< 0.001
Yes	52.8		64.1	
No	61.4		83.7	
Concomitant medication(s)		0.037		< 0.001
Yes	48.8		64.4	
No	62.9		85.0	
Interval from diagnosis to starting TKI therapy, month		0.096		< 0.001
< 6	60.8		83.3	
6–11	53.3		75.1	
12–24	61.5		59.3	
≥ 24	50.7		59.3	

Abbreviations: *CRAE* chronic renal adverse event, *CKD* chronic kidney disease, *TKI* tyrosine kinase inhibitor

moreover, there was no statistical difference in 24-h urine protein levels between the imatinib and nilotinib cohorts (Fig. 4a). The levels of urinary albumin-creatinine ratio (Fig. 4b) and urine osmolality (Fig. 4c) were stable in the two cohorts. However, urinary β_2-microglobulin values declined during the first 12 months and significantly increased later compared with the level at 12 months on TKI therapy in both two cohorts (Fig. 4d). Although there were no differences in urinary β_2-microglobulin levels at baseline ($P = 0.157$) and 12 months ($P = 0.237$) between the two cohorts, the levels were significantly higher at 36 months ($P = 0.042$) and 42 months ($P = 0.039$) in the imatinib cohort than in the nilotinib cohort.

In the 55 newly diagnosed CML-CP patients, 35 (64%) developed CRAE at a median time of 18 months (range of 3–66 months), and eight (15%) developed CKD at a median time of 30 months (range of 12–66 months). There were no significant differences in urinary β_2-microglobulin values and 24-h urine protein values between the patients who developed CRAE and those who did not. Elevated urinary β_2-microglobulin values were found in 6/8 (75%) patients, at a median time of 6 months (range of 3–36 months) before CKD occurred. Urinary β_2-microglobulin values in the patients who developed CKD were higher than those in patients who did not develop CKD at 18 months ($P = 0.008$) and at 36 months ($P = 0.053$) (Fig. 6a in the Appendix). There was no significant difference in the 24-h urine protein values between the two groups (Fig. 6b in the Appendix).

Patients receiving second- or third-line TKI therapies

A total of 139 patients received nilotinib ($n = 65$) or dasatinib ($n = 74$) as second- ($n = 113$) or third-line ($n = 26$) TKI therapies. Of these, 90 patients (65%) were male. The median age was 40 years (range of 18–82 years). A total of 21 patients (15%) had kidney-related comorbidity(ies). A total of 49 patients (35%) received previous non-TKI treatment. A total of 11 patients (8%) took concomitant medication(s). The median serum creatinine value was 71 μmol/L (range of 29–101 μmol/L) and the median eGFR value was 94 ml/min/

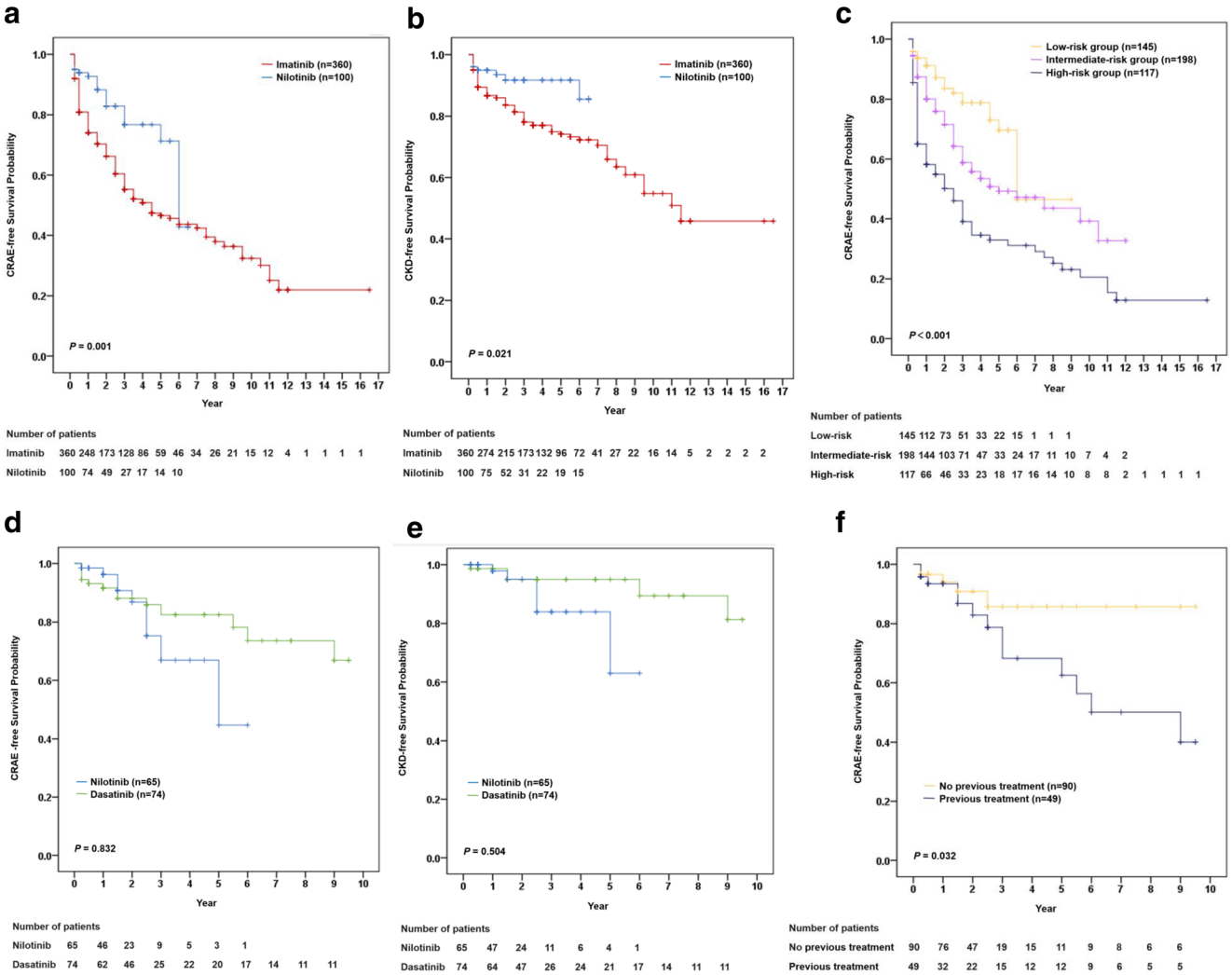

Fig. 3 CRAE-free survival and CKD-free survival rates in patients receiving first-line and second- or third-line TKI therapies. First-line TKI therapy: CRAE-free survival (**a**), CKD-free survival (**b**), CRAE-free survival by risk-group (**c**). Patients were divided into low-risk (≤ 1 factor), intermediate-risk (2 factors), and high-risk (≥ 3 factors) groups, based on four adverse factors, including imatinib use, male sex, age ≥ 50 years, and previous non-TKI treatment. There was no difference in the onset of CRAE between the two subgroups with 0 and 1 factors. Second- or third-line TKI therapy: CRAE-free survival (**d**), CKD-free survival (**e**), and CRAE-free survival by previous non-TKI treatment (**f**). CRAE, chronic renal adverse event; CKD, chronic kidney disease

1.73 m^2 (range of 62–257 ml/min/1.73 m^2) at baseline. There were no differences in patient characteristics between the two cohorts, despite a longer TKI therapy duration in the dasatinib cohort ($P < 0.001$) (Table 4). With a median follow-up of 24 months (range of 3–118 months), 86 (62%) patients achieved CCyR at a median time of 3 months (range of 3–84 months), 59 (42%) patients achieved MMR at a median time of 6 months (range of 3–90 months), and 29 (21%) patients achieved MR4.5 at a median time of 12 months (range of 3–66 months). There were almost no significant differences in the changes in eGFR and creatinine levels compared to baseline for both cohorts during TKI therapy (Fig. 2c, d).

In the nilotinib cohort, nine patients (14%) developed CRAE at a median time of 24 months (range of 3-60 months) and five patients (8%) developed CKD at a median time of 30 months (range of 12–60 months). In the dasatinib cohort, 13 patients (18%) developed CRAE at a median time of 18 months (range of 3–108 months), and five patients (7%) developed CKD at a median time of 18 months (range of 3–108 months). There were no significant differences in the probabilities of CRAE-free survival and CKD-free survival at 3 years between the nilotinib cohort (67%, 95% CI 45–89%; and 84%, 95% CI 68–99%) and the dasatinib cohort (83%, 95% CI 77–95%, $P = 0.832$; and 95%, 95% CI 90–100%, $P = 0.504$) (Table 5; Fig. 3d, e). Multivariate analysis showed that previous non-TKI treatment was an adverse factor affecting CRAE-free survival (Table 6). There were no differences in the onset of chronic renal injury between the nilotinib and dasatinib cohorts.

Table 3 Multivariate analyses for the onset of CRAE or CKD in patients receiving first-line TKI therapies

	CRAE			CKD		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex			0.026			< 0.001
Female						
Male	1.4	1.0–2.0		4.5	2.6–7.9	
Age, year			< 0.001			< 0.001
< 30 (ref)						
30–40	1.1	0.7–1.8	0.557	2.2	0.9–5.3	0.096
40–50	1.2	0.8–1.9	0.359	3.9	1.7–9.1	0.002
50–60	1.9	1.2–3.1	0.012	8.4	3.5–20.4	< 0.001
≥ 60	2.6	1.6–4.2	< 0.001	15.8	6.7–37.1	< 0.001
TKI			0.031			0.272
Nilotinib						
Imatinib	1.7	1.1–2.7		1.5	0.7–3.2	
Previous non-TKI treatment			0.029			0.313
No						
Yes	1.4	1.0–1.9		1.4	0.7–2.5	
Interval from diagnosis to starting TKI therapy, month			0.928			< 0.001
< 6 (ref)						
6–11	1.0	0.5–1.9	0.956	2.0	0.9–4.1	0.078
12–24	0.8	0.4–1.8	0.574	2.6	1.1–6.2	0.031
≥ 24	1.1	0.6–2.0	0.807	4.4	2.4–8.3	< 0.001

Abbreviations: *CRAE* chronic renal adverse event, *CKD* chronic kidney disease, *TKI* tyrosine kinase inhibitor

eGFR changes in patients switching from imatinib to second-generation TKIs

In the 27 patients with normal renal function that switched to nilotinib ($n = 8$) or dasatinib ($n = 19$) due to imatinib resistance rather than renal toxicity, four male patients experienced CRAE during imatinib therapy. The median age was 36 years (range of 28–59 years). None of these patients had kidney-related comorbidity(ies). The median interval from diagnosis to starting TKI therapy was 2 months (range of 0–9 months). The eGFR values significantly increased at 6 months after switching to either nilotinib ($n = 2$) or dasatinib (n = 2) therapy ($P = 0.037$) and recovered to normal levels. None of these patients developed CRAE again while undergoing nilotinib or dasatinib therapy until the end of the follow-up period (Fig. 5).

Discussion

To explore the chronic renal toxicity profiles of TKIs, we investigated CML-CP patients with normal renal function at baseline. Our study showed that imatinib use was significantly associated with chronic renal injury, likely due to increased renal tubular impairment compared with nilotinib use as a first-line TKI therapy. In addition, male sex, increasing age, previous non-TKI treatment, and longer interval from diagnosis to starting TKI therapy were factors significantly associated with more occurrences of chronic renal injury. In patients receiving nilotinib or dasatinib as second- or third-line TKI therapies, previous non-TKI treatment was significantly associated with the onset of CRAE; however, nilotinib and dasatinib had similar impacts on renal function. Furthermore, imatinib-related chronic renal injury could be reversed when patients switched to nilotinib or dasatinib therapy.

TKI-related renal dysfunction has been reported, and several studies have confirmed that imatinib is more likely to cause chronic renal injury than nilotinib and dasatinib. Marcolino et al. [1] reported that the long-term imatinib treatment may cause significant decreases in the eGFR, and 16% of the patients with normal renal function at baseline developed CKD with a median imatinib therapy duration of 4.5 years. Yilmaz et al. [2] examined the effects of the three TKIs on the renal functions of newly diagnosed CML patients and found that nilotinib and dasatinib had less chronic renal toxicity than imatinib.

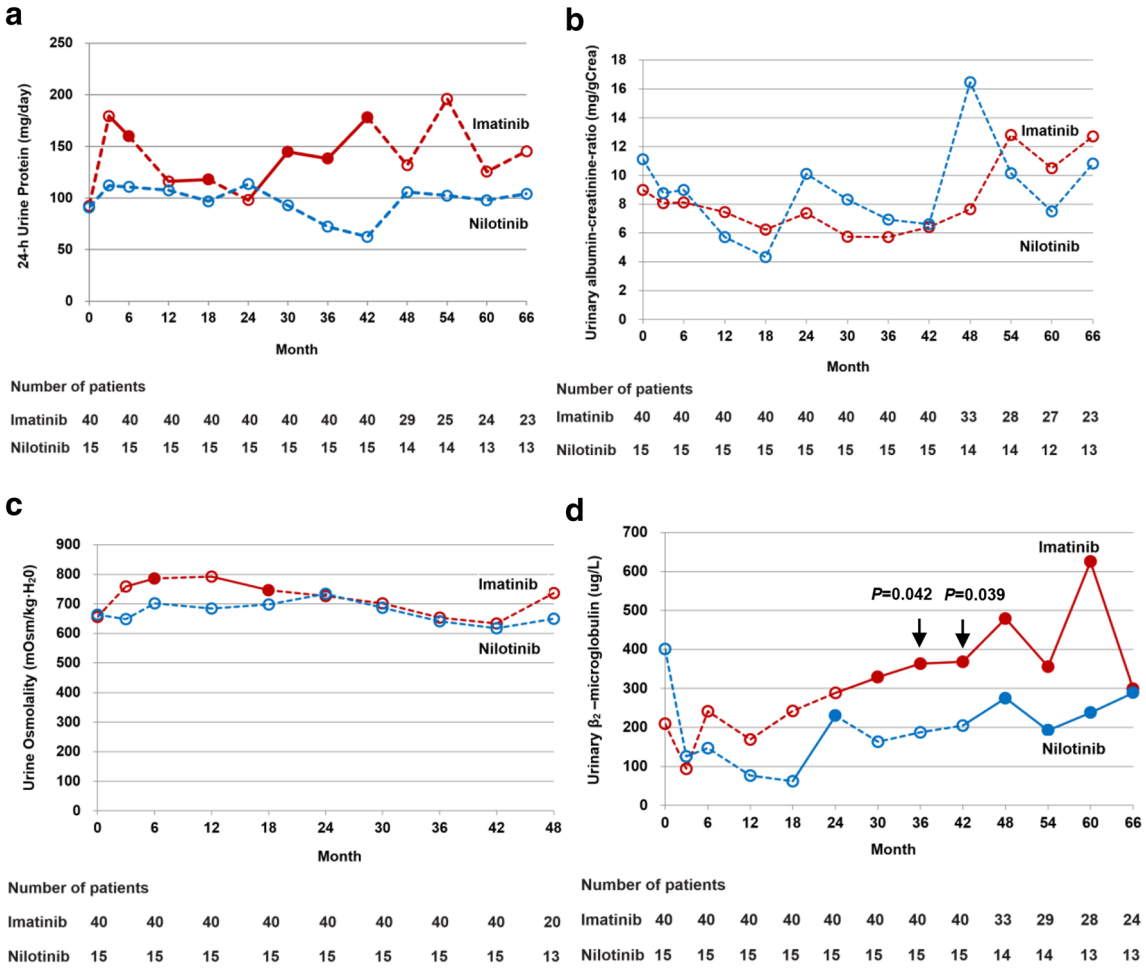

Fig. 4 Changes in 24-h urine protein (**a**), urinary albumin-creatinine ratio (**b**), urine osmolality (**c**), and urinary β_2-microglobulin (**d**) values in newly diagnosed patients receiving first-line TKI therapies. Significant differences were calculated by paired samples Student's *t* tests between values at baseline (**a**–**c**) or at 12 months (**d**) and each time point during TKI therapy. Solid line and dot indicate $P < 0.05$. Dotted line and circle indicate $P > 0.05$

Molica et al. [3] confirmed that patients who received imatinib showed a significant decline in eGFR values over time, although nilotinib was the only TKI associated with an increase in eGFR values. We confirmed TKI-related renal injury by using more sensitive and accurate assessment methods of renal function, including a 30% reduction from baseline in eGFR values and event-free survival rate (refers to CRAE- and CKD-free survival), because drug-related renal injury may develop over time. In general, imatinib induced more significant renal injury than nilotinib. The probability of CRAE-free survival at 6 years in the imatinib cohort (44%, $n = 46$) was similar to that in the nilotinib cohort (43%, $n = 10$) as first-line TKI therapy might be caused by limited patient number at that time point. Previously, two studies [2, 3] reported that nilotinib was the only TKI associated with an increase in eGFR values compared with imatinib and dasatinib. However, our current study showed that nilotinib generally induced a decrease in eGFR values when used as a first-, second-, or third-line therapy in all but two patients with imatinib-related CRAE that switched to nilotinib due to imatinib-resistance. Furthermore, Hino et al. [4] reported that switching from imatinib to a second-generation TKI could improve renal functions impaired by imatinib therapy. We did not find the significant changes of eGFR levels in the 27 patients switching from imatinib to a second-generation TKI except for the four patients who experienced CRAE during imatinib therapy and had an improvement in their renal function after switching to nilotinib or dasatinib.

Drug-induced renal toxicity may be caused by the impairment of glomerular filtration, tubular resorption, or interstitium [9, 10]. TKI-related renal injury has not been well-understood because eGFR levels reflect the entirety of glomerular, tubular, and interstitial function. Renal tubular cells are susceptible to the toxic effects of medications because tubular cells are exposed to high levels of toxins through the concentration and absorption of

Table 4 Clinical characteristics for the patients receiving second- or third-line TKI therapies

Characteristics	Nilotinib ($n = 65$)	Dasatinib ($n = 74$)	P
Male, no. (%)	40 (61.5)	50 (67.6)	0.458
Age, median (range), year	41 (18–74)	39 (19–82)	0.641
The starting dose of TKI (%), mg/d [no. (%)]	800 [29 (44.6)]/600 [36 (55.4)]	100 [74 (100.0)]	
Second-/third-line therapy, [no. (%)]	60 (92.3)/5 (7.7)	53 (71.6)/21(28.4)	0.002
WBC, median (range), $\times 10^9$/L	5.7 (2.1–54.6)	6.8 (2.6–247.0)	0.092
Hemoglobin, median (range), g/L	120 (64–164)	126 (48–186)	0.730
Platelets, median (range), $\times 10^9$/L	163 (24–2610)	176 (29–3923)	0.193
PB basophils, median (range), %	0 (0–19)	2 (0–19)	< 0.001
PB blasts, median (range), %	0 (0–12)	0 (0–12)	0.781
BM basophils, median (range), %	0 (0–13)	0 (0–18)	0.446
BM blasts, median (range), %	1 (0–14)	1 (0–14)	0.778
Baseline creatinine, median (range), μmol/L	70.0 (30.0–101.0)	72.5 (29.0–97.0)	0.094
Baseline estimated GFR, median (range), ml/min/1.73 m^2	95.3 (62.2–257.3)	90.7 (62.5–244.6)	0.179
Comorbidity(ies), no. (%)	8 (123)	13 (17.9)	0.928
Concomitant medication(s), no. (%)	5 (7.7)	6 (8.1)	0.486
Previous non-TKI treatment, no. (%)	21 (32.3)	28 (37.8)	0.496
TKI-dose reduction, no. (%)	11 (16.9)	7 (9.5)	0.191
Dose of TKI at the end of follow-up, mg/d [no. (%)]	800 [23 (35.4)]/600 [31(47.7)]/400 [11 (16.9)]	100 [67 (90.5)]/50 [7 (9.5)]	
Interval from diagnosis to starting current TKI therapy, median (range), month	25 (4–240)	36 (3–240)	0.933
Follow-up, median (range), month	18 (3–78)	28 (3–114)	< 0.001

glomerular filtrates [9, 10]. In the current study, we monitored glomerular and tubular function-related indexes in newly diagnosed patients with normal renal function on imatinib or nilotinib therapy. There was a significant increase in the 24-h urine protein levels after 6 months compared with the baseline in the imatinib cohort, but this finding was not observed in the nilotinib cohort. It can be speculated that imatinib rather than nilotinib, could result in a mild adverse impact on glomerular function over time. It is not clear whether a more remarkable increase on 24-h urine protein levels would be observed if the imatinib therapy duration was long enough or more patients were enrolled. Furthermore, a relatively stable level of urine osmolality during TKI therapy in the current study indicated no significant tubular damage induced by imatinib or nilotinib therapy. β_2-microglobulin is produced by all cells expressing MHC class I antigen, especially lymphocytes and tumor cells, and is readily filtered through the glomerulus and almost completely reabsorbed and destroyed by proximal tubular cells. It is well known that increasing urinary β_2-microglobulin levels is not only a more sensitive and earlier predictor of tubular dysfunction compared with abnormal urine osmolality but it is also a possible reflection of tumor load [11]. In the current study, the urinary β_2-microglobulin values were elevated in most of the patients (75%) before CKD occurred and were higher in the patients who developed CKD than in those who did not, which indicates that it is a significant predictor of early tubular dysfunction. Moreover, a high level of urinary β_2-microglobulin before starting TKI therapy may primarily be the result of a high leukemia load, and a significant decline during the first 12 months on TKI therapy was consistent with achieving cytogenetic and molecular responses. It has been speculated that the gradual increase in urinary β_2-microglobulin over time may be due to TKI-related tubular damage. The similar levels of urinary β_2-microglobulin at baseline and at 12 months in the imatinib and nilotinib cohorts and the abnormally higher levels at 36 months and 42 months in the imatinib cohort suggested that imatinib might cause more significant damage to renal tubules than nilotinib, which may explain the finding that chronic renal injury was more common in the imatinib cohort than that in the nilotinib cohort.

The molecular mechanism regarding TKI-related nephrotoxicity has not been thoroughly elucidated. Some studies revealed that TKI-related nephrotoxicity may be associated with the inhibition of PDGF-R signaling, which is expressed in glomeruli, arteries, renal tubules, and renal interstitial cells [12, 13]. Imatinib has a more specific inhibitory effect on PDGF-R, compared to C-KIT or BCR-ABL, than nilotinib and dasatinib [12], which might be one of the reasons for the more significant nephrotoxicity caused by imatinib than by nilotinib and dasatinib.

Table 5 Univariate analyses for CRAE-free survival and CKD-free survival rates at 3 years in patients receiving second- or third-line TKI therapies

	CRAE-free survival		CKD-free survival	
	%	*P*	%	*P*
Sex		0.386		0.170
Male	75.6		90.1	
Female	81.6		95.5	
Age, year		0.694		0.933
< 30	82.3		95.0	
30–40	89.3		91.9	
40–50	69.0		90.8	
50–60	81.6		93.8	
≥ 60	73.3		80.0	
TKI		0.832		0.504
Dasatinib	82.5		95.1	
Nilotinib	66.9		84.0	
TKI using		0.543		0.814
Third-line	62.2		92.3	
Second-line	82.4		91.4	
Previous non-TKI treatment		0.032		0.173
Yes	68.2		90.4	
No	85.7		92.7	
Comorbidity(ies)		0.583		0.113
Yes	81.6		86.7	
No	77.1		92.7	
Concomitant medication(s)		0.391		0.660
Yes	77.9		87.5	
No	78.2		92.2	
Interval from diagnosis to starting TKI therapy, month		0.762		0.712
< 6	83.0		94.1	
6–11	92.0		95.5	
12–24	73.3		100.0	
≥ 24	75.1		88.2	

Abbreviations: *CRAE* chronic renal adverse event, *CKD* chronic kidney disease, *TKI* tyrosine kinase inhibitor

The PDGF-β/PDGF-R axis plays an important role in the regeneration of tubular cells after acute tubular necrosis in animal models [14]. In addition, the inhibition of the PDGF-β/PDGF-R axis can reduce interstitial fibrosis in ischemia-reperfusion mouse models [15]. PDGF has commonly been implicated in the pathogenesis of progressive kidney injury in human disease and experimental models [13]. Several animal model tests have found that the inhibition of PDGF after an injury is associated with an improvement in renal function. PDGF appears to play a crucial role in stimulating the extracellular matrix synthesis and the mesangial cell proliferation that may promote kidney damage, with the subsequent occurrence of nephropathies [16–18]. These results were in accordance with the findings observed in some study that patients treated with nilotinib experienced an improvement in eGFR values [2, 3].

We found that the male sex was associated with the onset of chronic renal injury, which has not been reported before. Similar to previously reported studies [2], increasing age was linked with the onset of declining eGFR values and CRAE during TKI therapy in the current study. It is easy to understand that longer-term previous treatment contributed to the development of CRAE. However, Molica et al. [3] reported that imatinib may induce changes in eGFR values, which may contribute to the onset of ischemic events, whereas none of the patients developed cardiovascular events in our study.

Our study has some limitations: (1) there were certain differences in the baseline characteristics between the cohorts, such as the longest interval from the diagnosis of CML in the dasatinib cohort, the highest eGFR levels in the nilotinib cohort at baseline, and varied follow-up periods among the cohorts receiving different TKIs in the

Table 6 Multivariate analyses for the onset of CRAE or CKD in patients receiving second- or third-line TKI therapies

	CRAE			CKD		
	HR	95% CI	*P*	HR	95% CI	*P*
TKI			0.342			0.091
Dasatinib						
Nilotinib	1.5	0.6–3.8		3.5	0.8–14.7	
Previous non-TKI treatment			0.040			0.234
No						
Yes	2.5	1.0–5.8		2.2	0.6–8.0	
Comorbidity(ies)			0.421			0.083
No						
Yes	1.5	0.6–3.9		3.2	0.9–11.8	

Abbreviations: *CRAE* chronic renal adverse event, *CKD* chronic kidney disease, *TKI* tyrosine kinase inhibitor

retrospective study; (2) we did not analyze the impact of dasatinib on renal functions as a first-line TKI therapy because dasatinib has not yet been approved as a first-line therapy for CML-CP patients in China; and (3) there were relatively few cases receiving TKI as a third-line therapy that may influence the outcome of statistical analyses.

In conclusion, imatinib treatment was significantly correlated to chronic renal injury, and possibly associated with glomerulus and renal tubular injury, as a first-line TKI therapy in CML-CP patients. However, nilotinib and dasatinib had similar mild adverse impacts on renal function as second- or third-line therapies. Renal function should be monitored in patients receiving imatinib therapy and those with high risk

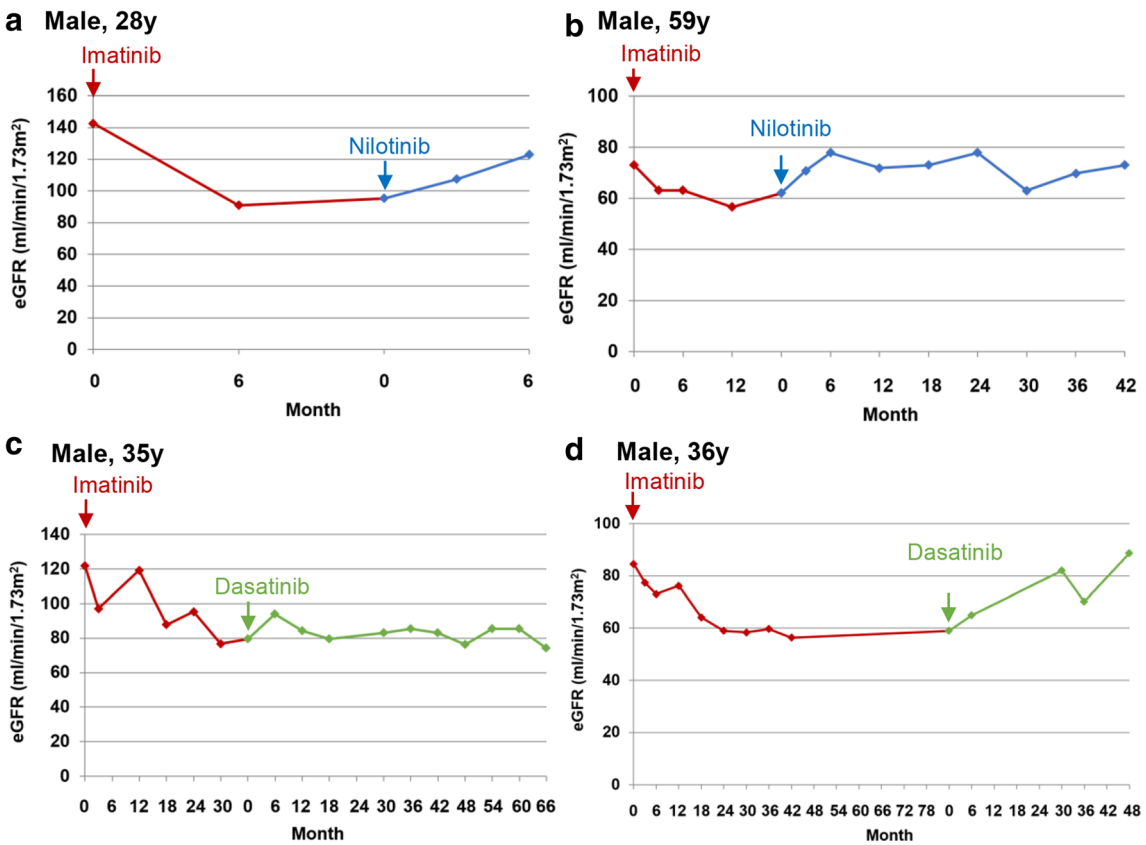

Fig. 5 eGFR value changes during nilotinib or dasatinib therapy in the patients who developed CRAE during imatinib therapy and switched to a second-generation TKI due to imatinib resistance

factors, such as male sex, increasing age, longer interval from diagnosis to starting TKI therapy, and previous non-TKI treatment. Imatinib-related chronic renal injury may be reversible and may be improved by switching to nilotinib or dasatinib.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

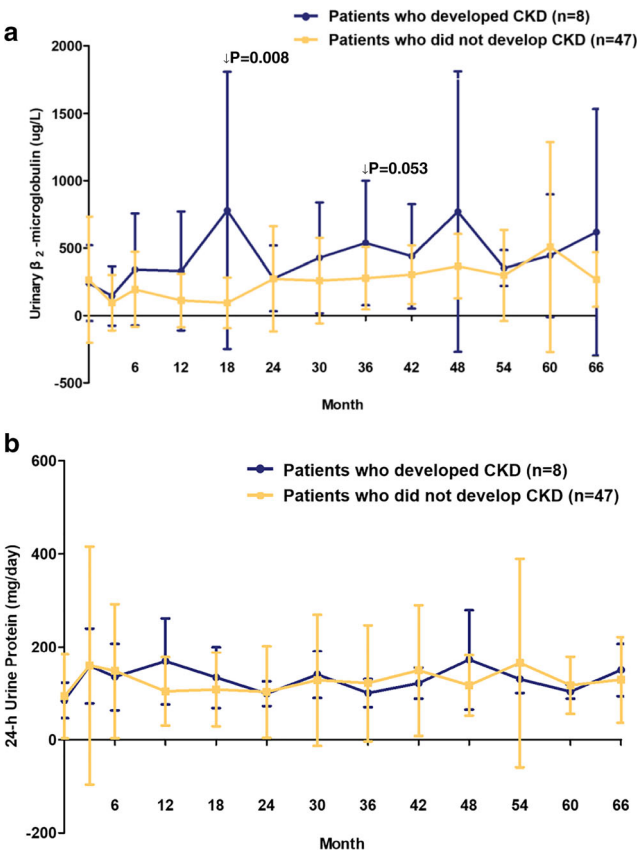

Fig. 6 Comparisons of urinary β_2–microglobulin (**a**) and 24-h urine protein (**b**) values between newly diagnosed patients receiving first-line TKI therapies that developed CKD and those that did not develop CKD

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