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Changes in estimate glomerular filtration rate associated with long-term tyrosine kinase inhibitor treatment in patients with chronic myelogenous leukemia

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Objective: Tyrosine kinase inhibitors (TKIs) have dramatically improved prognosis of chronic myelogenous leukemia (CML), and four kinds of TKIs are currently used for first-line treatment in Japan. Renal damage has been known as a major adverse effect of TKIs, but there are a few reports that describe frequency of renal damage induced by long-term administration of TKIs. Therefore, we retrospectively analyzed the incidence of renal dysfunction with a long-term use of TKIs.
Methods: Newly diagnosed 83 CML patients in chronic phase who were treated with TKIs for longer than 3 years were analyzed. Of those, 54 patients were treated with imatinib, 21 with dasatinib, and 8 with nilotinib. We examined chronological changes of the value of estimated glomerular filtration rate (eGFR) during TKI therapies. The value of eGFR was calculated using the equation for the Japanese population by the data from the J-CKDI (Japanese Association of Chronic Kidney Disease Initiatives).
Results: The median follow-up duration was 10.3 years in the imatinib cohort, 5.45 years in the dasatinib cohort, and 6.66 years in the nilotinib cohort. Imatinib was associated with higher incidence of renal dysfunction compared to dasatinib and nilotinib (P = 0.0061). After 5 years of treatment, reduction in the mean values of eGFR (ml/min/1.73 m^2) in the imatinib, dasatinib, and nilotinib groups were 20.22 (P < 0.0001), 10.26 (P = 0.0026), and 2.667 (P = 0.3105), respectively. Multivariate analyses revealed that treatment with imatinib and female gender were the significant risk factors for renal damage.
Conclusion: Long-term use of imatinib was significantly correlated with development of drug-induced renal damage compared with dasatinib and nilotinib.

Key words: chronic myelogenous leukemia, tyrosine kinase inhibitor, renal adverse effects, estimated glomerular filtration rate

Introduction

Chronic myelogenous leukemia (CML) is a type of myeloproliferative neoplasm characterized by the abnormal *BCR-ABL1* fusion gene. The fusion gene is generated by a chromosomal translocation t(9;22)(q34.1;q11.2) and a newly formed chromosome called Philadelphia (Ph) chromosome. The gene product of *BCR-ABL1* is a tyrosine kinase with an increased kinase activity and plays a central role in the pathogenesis of CML.[1] Tyrosine kinase inhibitors (TKIs) have dramatically improved the prognosis of CML, and they are currently used as standard first-line drugs.[2] Imatinib mesylate (IMA) (Glivec®, Gleevec™, Novartis) was the first TKI to be successfully used in the treatment of CML. IMA binds to the ATP-binding pocket of the BCR-ABL1 kinase and inhibits tyrosine kinase activity of the molecule.[3,4] IMA is generally well tolerated with fewer adverse events (AEs) than those with traditional cytotoxic agents, *e.g.*, cytarabine, interferons, hydroxyurea, and busulfan.

Currently, second-generation TKIs, *e.g.*, nilotinib hydrochloride (NIL) (Tasigna®, Novartis), dasatinib hydrate (DAS) (Sprycel®, Bristol-Myers Squibb), and bosutinib hydrate (BOS) (Bosulif®, Pfizer), have been developed, and these TKIs demonstrate efficacy even in

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cases with resistance or intolerance to IMA.[5-7] All of the TKIs are designed to inhibit ABL1 tyrosine kinase;[8] however, they have certain levels of off-target inhibitory effects on other kinases, *e.g.*, platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, c-kit, Src, DDR-1, DDR-2,[9,10] and the difference in the off-target profiles is thought to be related to the difference in the AEs of each TKI.

Among these AEs, renal damage has been reported in several studies.[7,11-16] These studies suggest that TKIs may reduce the estimated glomerular filtration rate (eGFR), and the AEs are more distinct with IMA than with other TKIs.[12-15] Because PDGFR is widely expressed on renal cells, and PDGFR plays an important role in tubular cell regeneration,[17-19] the renal AEs may be induced by the off-target inhibition of PDGFR by TKIs interfering with renal repairs. Cancer and anticancer therapies often affect renal function, and understanding how kidneys react oncologically is important in the treatment of cancers. This new field of science called onconephrology is currently attracting much attention.

Treatment with TKIs has enabled CML patients to survive for extended lengths of time. Therefore, it is most important to clarify long-term effects of TKIs on kidney function. Currently, 4 TKI drugs: IMA, NIL, DAS, and BOS, can be used as first-line drugs for CML;[20] however, the long-term effects of these TKIs on renal functions have not been fully understood.[13] Therefore, to elucidate the long-term effects of TKIs on renal functions, we retrospectively analyzed data of CML patients who were treated with IMA, NIL, and DAS, and we evaluated the long-term clinical outcomes in the renal functions of these patients.

Materials and Methods

Patients and study design

Medical records of 136 consecutive adult CML-chronic phase (CP) patients who received IMA, NIL, or DAS as the first-line TKI treatment at Kitasato University Hospital from January 2001 through December 2018 were retrospectively reviewed. All the patients were diagnosed with CML with either the Ph+ chromosome or *BCR-ABL1* transcripts in the peripheral blood or bone marrow cells. For the analyses, patients with eGFR ≤29 ml/min/1.73 m^2, in the accelerated phase or blast phase at the point of therapy initiation, were excluded. Patients who had a nephrectomy were also excluded. To evaluate the long-term AE profiles of the drugs, patients who were treated with TKIs for <3 years were also excluded from the study.

The primary endpoint of the study was eGFR changes in the clinical course. The secondary endpoint was renal event-free survival (EFS); a renal event was defined as ≥20 ml/min/1.73 m^2 of reduction of eGFR from the baseline, and renal EFS was defined as the duration, in months or in years, from the initiation of the TKI treatment to the onset of a renal event.

Observation of the patients was censored when the first-line TKI was stopped or switched to another TKI, or patients died, dropped out, or were transferred to other hospitals, or the disease progressed to the accelerated phase or the blast phase. In this study, values of eGFR were calculated using the 3-variable equation, proposed for the Japanese population by the J-CKDI (Japanese Association of Chronic Kidney Disease Initiatives): eGFR [ml/min/1.73 m^2] = 194 $\times$ serum creatinine$^{-1.094}$ $\times$ age$^{-0.287}$ $\times$ 0.739 [if female].[21] Because urinalytic data were lacking in many cases, renal damage was evaluated by blood tests, *e.g.*, eGFR.

This study was performed as a clinical study under the approval of the ethical committee of Kitasato University Hospital (B18-287).

Statistical analyses

Kruskal-Wallis and Mann-Whitney tests were used to evaluate statistical difference between each TKI group. Paired *t*-test was used to assess the difference of mean eGFRs between the baseline and each time point. We plotted EFS curves using Kaplan-Meier survival estimates. Log-rank tests were used to analyze survival data. Univariate and multivariate Cox proportional hazard models were used to identify the factors associated with the development of renal dysfunction. P-values of <0.05 were considered statistically significant. Statistical analyses were performed by using Prism software (version 8.4.3, GraphPad software, San Diego, CA, USA), and univariate and multivariate analyses were performed using StatMate software (version 5.01, ATMS, Tokyo).

Results

Patients' characteristics

Data on 136 patients were reviewed, and 53 patients were excluded from the analyses because of nephrectomy (n = 2), eGFR ≤29 ml/min/1.73 m^2 (n = 1), and <3 years of treatment with TKIs (n = 50) (Figure 1).

A total of 83 CML-CP patients were enrolled, among whom 54 patients were treated with IMA, 21 with DAS, and 8 with NIL as the first-line therapy (Figure 1). Patient characteristics are summarized in Table 1. In the IMA cohort, the median duration of observation was 123.7 months (range, 40－203 months), 52% were males, and

the median age was 53.3 years (range, 24－89 years). The baseline median eGFR level was 84.2 ml/min/1.73 m^2 (range, 43.8－130.2 ml/min/1.73 m^2). In the DAS cohort, the median duration of observation was 65.4 months (range, 37－114 months), 57% were males, and the median age was 57.8 years (range, 29－80 years). The baseline median eGFR level was 72.1 ml/min/1.73 m^2 (range, 48.2－100 ml/min/1.73 m^2). In the NIL cohort, the median duration of observation was 79.9 months (range, 60－93 months), 75% were males, and the median age was 54.4 years (range, 19－74 years). The baseline median eGFR level was 72.8 ml/min/1.73 m^2 (range, 31－107.8 ml/min/1.73 m^2). The patient characteristics of age, gender, and median baseline eGFR levels were not significantly different among the cohorts. The comorbidities of hypertension, diabetes mellitus, and hyperlipidemia in these cohorts were also similar. However, the duration of the TKI treatment was significantly longer in the IMA cohort ($P < 0.0001$) (Table 1).

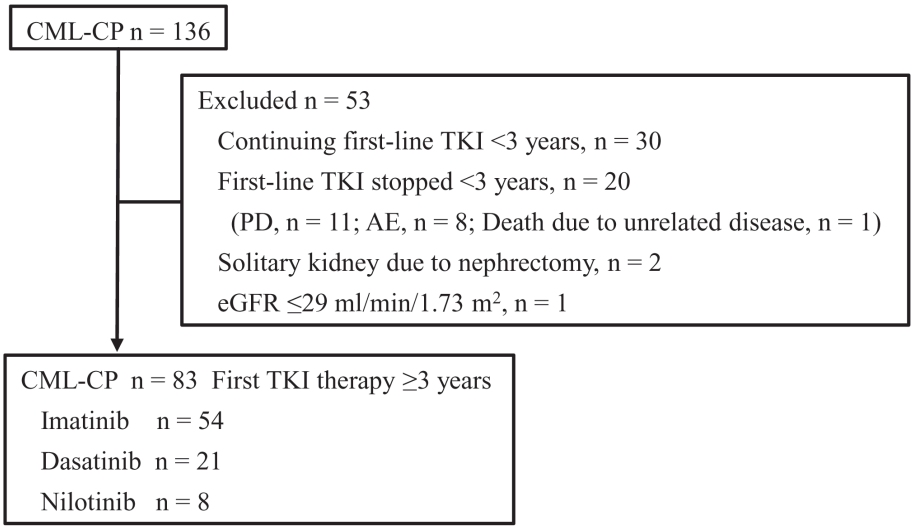

Figure 1. Patients and therapy

CML-CP, chronic myelogenous leukemia in chronic phase; TKI, tyrosine kinase inhibitor; PD, progressive disease; AE, adverse event; eGFR, estimated glomerular filtration rate

Table 1. Patients' clinical characteristics

Characteristics	Imatinib (n = 54)	Dasatinib (n = 21)	Nilotinib (n = 8)	P value
Age, median (range), years	53.3 (24－89)	57.8 (29－80)	54.4 (19－74)	0.5390
Gender, n (%)				0.4662
Male	28 (52.0)	12 (57.0)	6 (75.0)	
Female	26 (48.0)	9 (43.0)	2 (2.05)	
eGFR, median (range)	84.2 (43.8－130.2)	72.1 (48.2－100.0)	72.8 (31－107.8)	0.0720
Patients with impaired renal function (eGFR <60) at baseline (%)	7 (12.9)	5 (23.8)	2 (25.0)	0.9968
Comorbidities (%)				
Any comorbidities	24 (45.2)	14 (66.7)	6 (75.0)	0.0973
Hypertension	11 (20.3)	5 (23.8)	3 (37.5)	0.5606
Diabetes mellitus	8 (14.8)	3 (14.3)	3 (37.5)	0.3187
Hyperlipidemia	14 (25.9)	10 (47.6)	4 (50.0)	0.1237
Median follow-up duration (range, months)	123.7 (40－203)	65.4 (37－114)	79.9 (60－93)	<0.0001*

eGFR, estimated glomerular filtration rate
Data calculated with the Kruskal-Wallis test
*Significant difference

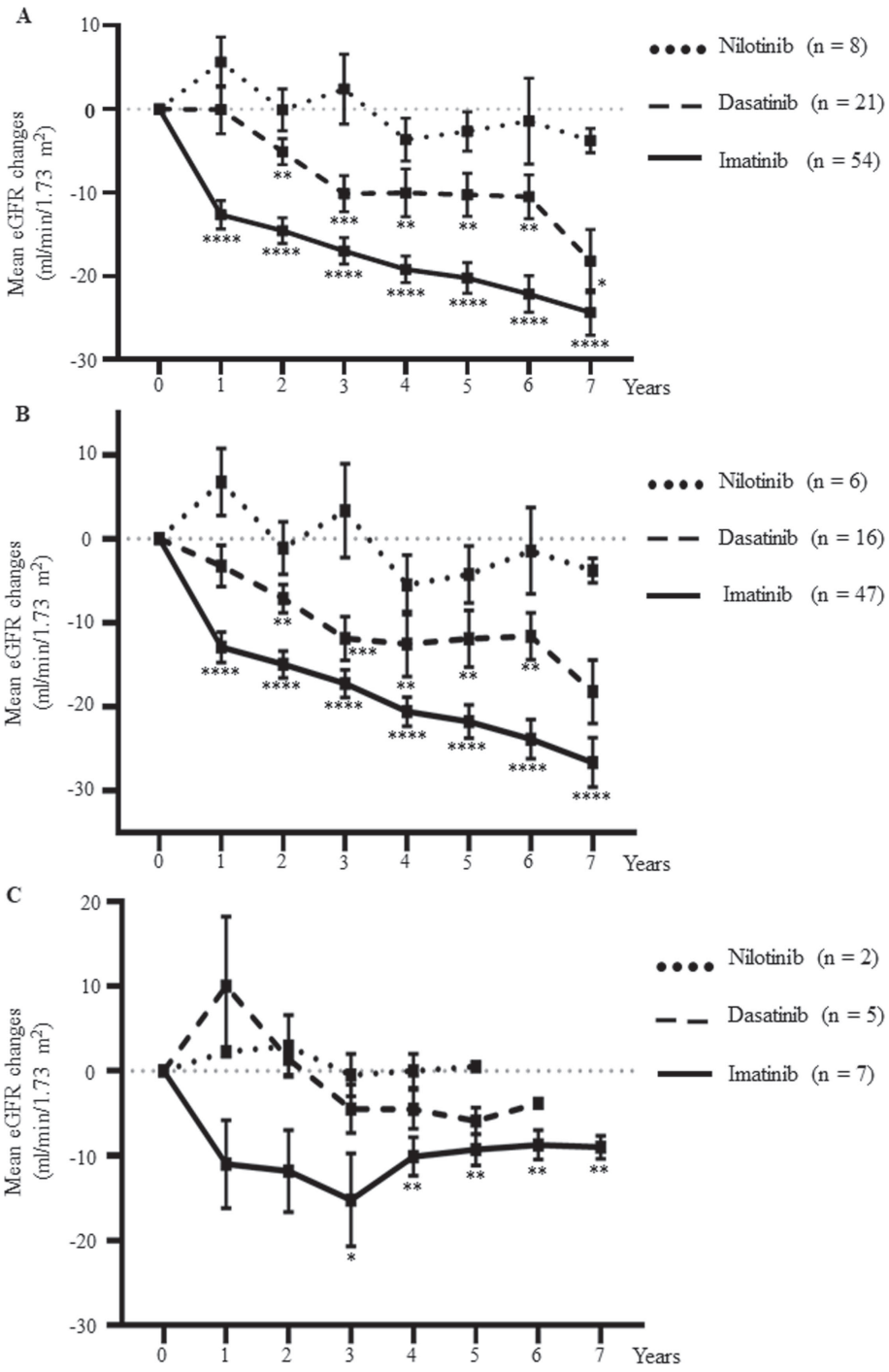

Figure 2. Mean eGFR changes from baseline

A. All CML-CP patients (n = 83)
B. CML-CP patients with normal renal function at baseline (n = 69)
C. CML-CP patients with impaired renal function at baseline (n = 14)
CML-CP, chronic myelogenous leukemia in the chronic phase
Data calculated with the paired *t*-test between the baseline and each time point
eGFR, estimated glomerular filtration rate
*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001

Changes in the eGFR values in each TKI cohort

We analyzed the changes of the eGFR values in each TKI cohort. As a result, the mean eGFR values in the IMA and DAS cohorts showed gradual decreases, but that in the NIL cohort remained stable. In the IMA cohort, eGFR levels were significantly reduced in all the observation periods compared with that at the baseline ($P < 0.0001$), with the mean eGFR reduction after 5 years of treatment of 20.22 ml/min/1.73 m^2 ($P < 0.0001$) (Figure 2A). In the DAS cohort, the mean value of the eGFR reduction after 5 years was 10.26 ml/min/1.73 m^2 ($P = 0.0026$). The reduction of the eGFR values was more prominent in the IMA cohort compared with that in the DAS cohort. On the other hand, eGFR levels in patients treated with NIL did not change significantly, and the mean reduction at the 5-year point was 2.67 ml/min/1.73 m^2 ($P = 0.3105$).

To evaluate the impact of the pretreatment renal

Table 2. Clinical characteristics of the patients with impaired renal function (eGFR <60 ml/min/1.73 m^2) at baseline

Characteristics	Imatinib (n = 7)	Dasatinib (n = 5)	Nilotinib (n = 2)	P value
Age, median (range), years	72.1 (58－89)	66.2 (56－80)	62 (50－74)	0.4977
Gender, N (%)				>0.9999
Male	6 (85.7)	4 (80.0)	2 (100.0)	
Female	1 (14.3)	1 (20.0)	0 (0.0)	
eGFR, median (range)	52.57 (43.8－58.9)	53.46 (48.2－58.8)	45 (31－59)	0.9006
Comorbidities (%)				
Any comorbidities	4 (57.1)	4 (80.0)	2 (100.0)	0.4406
Hypertension	3 (42.9)	1 (20.0)	1 (50.0)	0.7902
Diabetes mellitus	2 (28.6)	1 (20.0)	1 (50.0)	>0.9999
Hyperlipidemia	1 (14.3)	4 (80.0)	0 (0.0)	0.0385*
Median follow-up duration (range, months)	100.4 (55－155)	64.0 (42－82)	64.5 (60－69)	0.1456

Data calculated with the Kruskal-Wallis test
eGFR, estimated glomerular filtration rate
*Significant difference

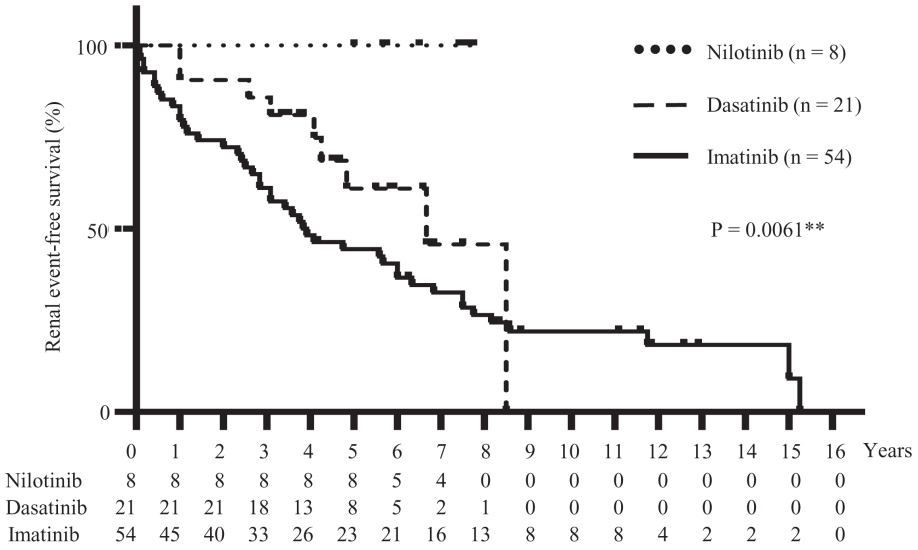

Figure 3. Renal EFS in patients with first-line TKI therapy

Median survival was 3.91 years (47 months) with imatinib, 6.67 years (80 months) with dasatinib, but not reached with nilotinib.
Data calculated with the Log-rank (Mantel-Cox) test
EFS, event-free survival; TKI, tyrosine kinase inhibitor
**P < 0.01

function on the posttreatment renal outcome, we analyzed changes in the eGFR values in patients with normal (eGFR ≥60 ml/min/1.73 m^2) (Figure 2B) or impaired renal function at baseline (eGFR <60 ml/min/1.73 m^2) (Figure 2C).

Figure 2B shows the renal outcomes in patients with normal renal function at baseline. In these patients, treatment with IMA and DAS significantly reduced eGFR levels ($P < 0.0001$, $P < 0.001$, respectively), but treatment with NIL did not show a significant reduction. The mean eGFR reductions from baseline after 5 years of treatment in the IMA, DAS, and NIL cohorts were 21.75, 11.9, 4.25 ml/min/1.73 m^2, respectively.

On the other hand, in patients with impaired renal function at the initiation of the TKI treatment, reduction of eGFR was less than that observed in patients with normal renal function, and significant reduction was observed only in patients treated with IMA ($P < 0.01$) (Figure 2C). Treatment with NIL did not show any obvious reductions of eGFR. The mean eGFR changes from the baseline after 5 years in the IMA, DAS, and NIL cohorts were -9.28, -5.9, and 0.5 ml/min/1.73 m^2, respectively (Figure 2C). Characteristics of the patients with impaired renal function at baseline were similar among all three TKI cohorts (Table 2).

Renal EFS in each TKI cohort

To evaluate the onset and factors that affect TKI-induced renal damage, we analyzed the renal EFS in patients treated with TKIs. In the analyses, we defined a renal event as ≥20 ml/min/1.73 m^2 reduction of eGFR. As a result, the median renal EFS in the IMA, DAS, and NIL cohorts were 3.91 years, 6.67 years, and not reached, respectively, and a significant difference was found among these TKI cohorts ($P = 0.0061$) (Figure 3). These results indicate that treatment with IMA is related to a higher risk of early renal dysfunction.

To evaluate the clinical factors associated with TKI-induced renal events, we performed univariate and multivariate analyses (Table 3). Univariate analysis showed that normal renal function at baseline was the primary risk factor for renal damage with a hazard ratio (HR) of 4.57 (95% CI 1.42－14.7, $P < 0.05$). Treatment with IMA and female gender were the secondary risk factors with HRs of 2.69 and 2.47 (95% CI 1.30－5.58, $P < 0.01$; 95% CI 1.40－4.38, $P < 0.01$), respectively. In the multivariate analysis, treatment with IMA and female gender remained significant as risk factors for the development of renal damage, and HRs were 2.34 and 2.46 (95% CI 1.12－4.87, $P < 0.05$; 95% CI 1.34－4.51, $P < 0.05$), respectively. Noteworthy, multivariate analysis showed that normal renal function at baseline showed a high risk of renal damage with an HR of 3.22, however, the difference was not statistically significant (95% CI 0.96－10.81, $P = 0.058$). This might be partly due to a bias in the number of patients. Those with impaired and normal renal function at baseline were 14 and 69 patients, respectively.

Table 3. Univariate and multivariate analysis of renal EFS in patients with TKI therapy

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Imatinib	2.6936 1.299－5.582	0.007698*	2.336 1.1224－4.865	0.0232*
Normal renal function at baseline (eGFR ≥60)	4.5781 1.4232－14.726	0.01071*	3.222 0.960－10.811	0.058
Age <60 years	1.4098 0.779－2.485	0.235	1.337 0.731－2.444	0.3444
Female gender	2.4733 1.3974－4.3775	0.0018*	2.458 1.339－4.512	0.0036*
No comorbidities	1.526 0.8838－2.635	0.1292	1.563 0.881－2.771	0.126

EFS, event-free survival; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate

*Significant difference

Renal dysfunction in patients treated with IMA

Our data showed that treatment with IMA was associated with a higher risk of renal damage. Therefore, we evaluated the clinical factors that were related to renal damage in the patients treated with IMA. Renal EFS stratified with renal function at baseline showed that normal renal function at baseline was a significant factor for a shorter EFS with an HR of 3.25 (95% CI 1.54－6.88, P < 0.05) (Figure 4A). The median EFS in patients with normal and impaired renal function at baseline was 3.58 years and not reached, respectively. In this analysis, female gender was also a significant risk factor for renal AEs. The median EFS in female and male patients were 2.96 and 6 years, respectively, with an HR of 1.98 in females (95% CI 1.07－3.68, P < 0.05) (Figure 4B). These results show that in patients treated with IMA, renal AEs will be significantly more in patients with normal renal function and female patients. Multivariate

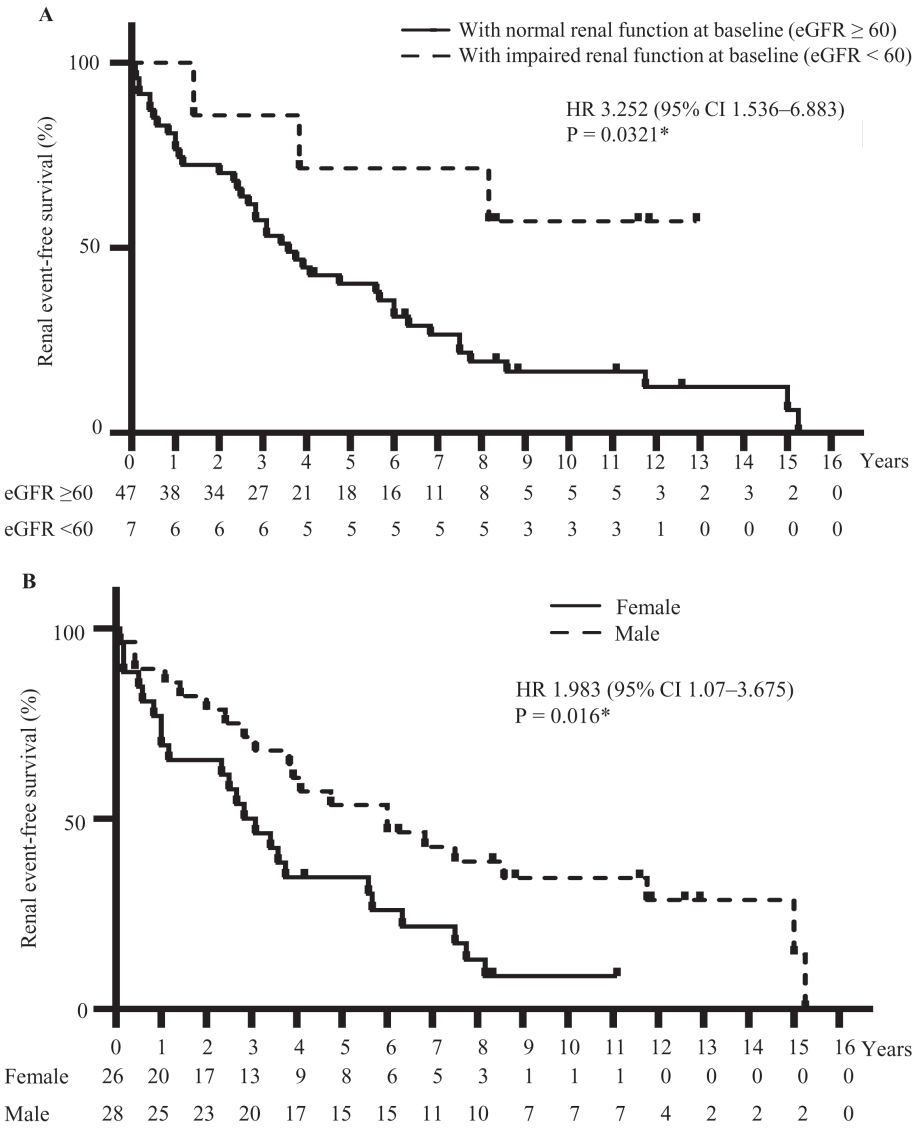

Figure 4. Renal EFS in patients with first-line imatinib therapy

A. Renal EFS stratified by renal function at baseline

Median survival: 3.58 years (43 months) with normal renal function at baseline (eGFR ≥60), not reached with impaired renal function at baseline eGFR <60)

B. Renal EFS stratified by gender

Median survival: females, 2.96 years (35.5 months); males, 6 years (72 months)

Data calculated with the Log-rank (Mantel-Cox) test

HR, hazard ratio; CI, confidence interval; EFS, event-free survival; eGFR, estimated glomerular filtration rate

*Significant difference

Table 4. Univariate and multivariate analysis of renal EFS in patients with imatinib therapy

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P Value	HR (95% CI)	P value
Normal renal function at baseline (eGFR ≥60)	3.356 1.029－10.94	0.044*	2.405 0.6858－8.436	0.17
Age <60 years	1.776 0.933－3.381	0.08	1.5924 0.764－3.318	0.213
Female gender	2.116 1.13－3.965	0.019*	2.24 1.150－4.374	0.017*
No comorbidities	1.578 0.853－2.917	0.145	1.794 0.936－3.438	0.078
Dosage of imatinib ≥400 mg	1.263 0.683－2.333	0.455	0.99 0.500－1.961	0.977

EFS, event-free survival; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate
*Significant difference

Table 5. Mean imatinib dose

Characteristics	Imatinib mg/day	P value
Dosage		<0.0001*
High (≥400 mg/day)	421.2	
Low (<400 mg/day)	270.8	
Gender		0.539
Male312.2		
Female347.6		
eGFR at baseline		0.0886
<60 ml/min/1.73 m^2	268.0	
≥60 ml/min/1.73 m^2	338.4	
Mean eGFR reduction		0.6293
≥20 ml/min/1.73 m^2	334.0	
<20 ml/min/1.73 m^2	308.6	

Data calculated with the Mann-Whitney test
eGFR, estimated glomerular filtration rate
*Significant difference

analysis showed that also in the IMA-treated subgroup, female gender was an independent risk factor for renal damage with an HR of 2.24 (95% CI 1.15－4.37, P < 0.05) (Table 4). Interestingly, the different dosages of IMA did not affect the development of renal dysfunction. The HR for renal AEs in the higher-dose group (≥400 mg/day) of IMA treatment over that of the lower-dose group (<400 mg/day) of IMA treatment was 0.99 (95% CI 0.5－1.96, P = 0.977). Moreover, the mean dosage of IMA was not significantly different between male and female patients, or between those with normal or impaired renal function at baseline (Table 5).

Discussion

Treatment with TKIs has remarkably prolonged the survival of CML patients, and this means that physicians must pay extra careful attention to the potential long-term toxicity of these drugs. Our analyses showed that treatment with IMA or DAS, especially IMA, was more frequently associated with renal AEs than was that with NIL. In addition, we found that the absence of renal impairment before treatment and female gender might be significant risk factors for developing renal dysfunction. The average rate of eGFR decline with age in the Japanese population has been reported to be 0.36 ml/min/1.73 m^2 per a year.[22] Compared to the data, 5-year eGFR declines of 20.22 ml/min/1.73 m^2 and 10.26 ml/min/1.73 m^2 in patients treated with IMA and DAS, respectively, are remarkably high.

Regarding the results in the present study, Yilmaz et

al.[13] have reported similar findings of 468 patients treated with IMA, NIL, and DAS who had been enrolled in their prospective clinical study. They showed that treatment with IMA, absence of renal dysfunction at baseline, advanced age, and history of hypertension or diabetes were significantly related to the development of renal dysfunction.

Molecular mechanisms of renal damage caused by TKIs have not been completely understood. However, a previous report has suggested that the toxic effects of IMA may be related to renal tubular damage and inhibition of PDGFR signaling pathways.[23] It has been shown that PDGFR is mainly expressed on renal tubules and, to a lesser extent, in the glomerulus, and expression of PDGFR mRNA is enhanced after ischemic renal injury.[17] Furthermore, the PDGFβ/PDGFR axis could be significantly involved in renal tubular cell regeneration after acute tubular necrosis in animal models.[18] These findings suggest that PDGFR play important roles in the restoration of damaged renal tubules. TKIs inhibit PDGFRα or PDGFRβ as an off-target effect, and IMA is known to have comparatively strong inhibitory effects on PDGFR. Half the maximal inhibitory concentrations of IMA to PDGFR, c-KIT, and BCR-ABL1 were 72 nM, 90 nM, and 211 nM, respectively.[24] These results suggest that IMA could induce renal dysfunction by disturbing tubular restoration through PDGFR inhibition. In the present study, we found no dose effects of IMA on the development of renal damage. Lower doses (<400 mg/day) and higher doses (≥400 mg/day) of IMA similarly induced eGFR reductions. These findings indicate that the IMA dosage did not affect the reduction of eGFR, and physicians should be aware that even lower doses of IMA could cause renal impairment.

From the viewpoint of off-target inhibition of tyrosine kinases, NIL is known as a selective TKI for BCR-ABL1 with fewer off-target effects. Iyoda et al.[25] reported that rats with experimental renal disease have less proteinuria and reduced glomerulosclerosis when treated with NIL. This observation is consistent with our observation that patients treated with NIL only had slight renal damage.

In the present study, we found that female gender was an independent risk factor for TKI-induced renal dysfunction. In accordance with the present study, in a previous prospective study by Yilmaz et al.,[13] a multivariate analysis revealed that female gender had a tendency for developing renal dysfunction (HR = 1.5; 95% CI 0.7－2.9, P = 0.288), although the difference was not statistically significant, and the data indicate that gender could be an important factor for TKI-induced renal damage. The underling mechanism for this gender difference has not been clarified; therefore, the impact of gender difference on TKI-induced renal damage warrants further investigation.

Notably, patients with renal dysfunction at baseline showed no significant reduction in eGFR during treatment with DAS or NIL, and only a modest decrease with IMA. Yilmaz et al.[13] have also reported a similar observation that patients with renal dysfunction at baseline showed less renal damage after treatments with TKIs. This is an interesting finding, however the underlying mechanism is still not well-understood and requires further clarification.

Although, at this time, we cannot explain clearly why female gender and normal renal function at baseline are independent risk factors for TKI-induced renal damage, it has been reported that trough plasma concentration of TKI is associated with efficacy and toxicity.[26] Recent approval of therapeutic drug monitoring for IMA in Japan has enabled us to monitor drug concentrations, and therefore further investigation on the association of drug concentrations and observed risk factors are warranted.

Moreover, it is known that increasing urinary β2-microglobulin (β2-MG) is a predictor for tubular dysfunction. Ren et al.[15] reported that patients who developed renal dysfunction after treatment with TKIs had higher urinary β2-MG levels than those who did not. It has been speculated that the gradual increase in urinary β2-MG may be due to TKI-induced tubular damage. It may be meaningful to evaluate the significance of urinary β2-MG as an early predictor for renal damage in the treatment with TKIs.

In conclusion, the present study demonstrated that long-term treatment with IMA and DAS, especially IMA, was significantly associated with renal adverse effects, and several associated risk factors were revealed. These results strongly suggest that when TKIs are administered for the treatment of CML, physicians should regularly monitor the patient's eGFR and, according to the TKIs prescribed, be especially cautious of the risk of renal damage.

Conflicts of Interest: None

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