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ORIGINAL ARTICLE

Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia

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Abstract

Knowledge of the toxicity profile of long-term treatment with imatinib is limited. In the present study, we sought to evaluate renal function and hemoglobin levels during long-term imatinib treatment. Eighty-two patients with chronic myelogenous leukemia in chronic phase who had been on imatinib for over 5 years were retrospectively analyzed. The mean estimated glomerular filtration rate (eGFR) was significantly decreased over 5 years (77 ± 17 to 62 ± 14 ml/min/1.73m², $P < 0.001$). Higher age and lower eGFR value at initiation of imatinib were significantly associated with development of renal dysfunction by multivariate analyses. Mean hemoglobin levels also significantly decreased over the 5-year period (12.9 ± 1.7 to 12.4 ± 1.3 g/dl, $P < 0.01$). The rate of decrease in eGFR correlated significantly with hemoglobin levels (correlation coefficient $= -0.249$, $P < 0.05$). Serum erythropoietin (EPO) levels did not increase in 16 patients with both renal dysfunction and anemia (median, 31.9 mIU/ml). In patients who participated in a clinical trial of imatinib discontinuation, mean eGFR (50.0 ± 6.5 to 56.0 ± 10.2 ml/min/1.73m², $P < 0.05$) and hemoglobin levels (12.0 ± 1.7 to 14.0 ± 1.6 g/dl, $P < 0.01$) improved significantly at 1 year after discontinuation. These findings suggest that long-term imatinib results in a partially reversible continuous decline in renal function and decreased hemoglobin levels.

Keywords Chronic myelogenous leukemia · Imatinib · Renal dysfunction · Anemia

Introduction

Tyrosine kinase inhibitor (TKI) treatment has dramatically improved the outcome of chronic myelogenous leukemia (CML) in chronic phase (CP) [1]. Imatinib mesylate was the first TKI introduced and successfully used for the treatment of CML. In the long-term follow-up data of the International Randomized Study of Interferon and STI571 study, the rate of estimated overall survival with imatinib was 83.3% at 10 years [2]. Although several clinical trials recently demonstrated that TKIs can be discontinued in a proportion of patients who achieve a durable molecular remission [3–6], a majority of patients remain on long-term treatment with these agents in clinical practice. Imatinib is generally well-tolerated; common short-term adverse events include fluid retention, muscle cramp, gastrointestinal symptoms and skin rash [7, 8]. Recently, two studies reported a possible association of long-term imatinib treatment with renal dysfunction in patients with CML in CP [9, 10]. In addition, there has been one report of chronic anemia associated with imatinib treatment [11]. A relationship between renal dysfunction and anemia—namely renal anemia—has been well recognized. We hypothesized that renal dysfunction could play an important role in the development of anemia under imatinib treatment. Therefore, we retrospectively assessed the effect of long-term imatinib treatment on both renal dysfunction and anemia to elucidate their relationship in patients with CML.

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Patients and methods

Patients and treatment

Patients with CML in CP who had been treated with only imatinib for 5 years or longer at Keio University Hospital (Tokyo, Japan) were selected and retrospectively analyzed. This retrospective study was approved by the ethics committee of Keio University School of Medicine. At diagnosis, all patients were evaluated with complete blood counts with differentials and bone marrow examination, including cytogenetic analysis. The CP was defined by the presence of less than 15% blasts, less than 20% basophils, and less than 30% blasts plus promyelocytes in the peripheral blood and marrow [12, 13]. Patients were basically followed every 1–2 weeks for the first 2–3 months, then every 1–3 months, and underwent blood tests, including complete blood counts and biochemical data at each follow-up. All data including the patient characteristics, laboratory data and results of imatinib treatment were collected from the institutional database and medical records. Imatinib had been started at a daily dose of 400 mg, and the dose was adjusted at the discretion of each physician based on its toxicity, if necessary. A proportion of patients who remained in complete molecular remission for more than 2 years participated in an institutional TKI discontinuation trial.

Laboratory data and definitions

As universally available laboratory data, we applied the estimated glomerular filtration rate (eGFR) to assess the renal function in this study. EGFR was calculated using the formula of the Modification of Diet in Renal Disease equation for Japanese defined by the Japanese Society of Nephrology [14]. Chronic kidney disease (CKD) was defined as eGFR less than 60 ml/min/1.73 m^2 persisting for at least 3 months according to a published guideline, in which the definition fulfilled the criteria of stage 3 or higher CKD [15]. Anemia was defined as a hemoglobin level less than 13.5 g/dl for males and less than 11.5 g/dl for females according to the institutional criteria.

Statistical analysis

Serial changes of eGFR were assessed by repeated-measure analysis of variance (ANOVA). Univariate analysis was performed with Fisher's exact tests or Mann–Whitney *U* test as appropriate. Multivariate analysis was performed with multiple regression analysis to evaluate the factors associated with the development of CKD in patients without CKD upon imatinib initiation. Correlation between the decrease rate of eGFR and hemoglobin levels was evaluated using Pearson's product–moment correlation. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed with EZR, which is a graphical user interface for R [16].

Results

Patients

In total, 82 patients were evaluable and enrolled into the analysis. Patient characteristics at imatinib initiation are shown in Table 1. The median age at imatinib initiation was 49.5 years old. The mean baseline eGFR at imatinib initiation was 77 ml/min/1.73 m^2, and in 12 (15%) patients the eGFR was below 60 ml/min/1.73 m^2 and thus CKD was diagnosed. The median duration of imatinib treatment was 105 months, with a range of 60–170 months. The initial dose of imatinib was 400 mg/day in all patients, and the dose was reduced in 8 patients due to leukocytopenia ($N=5$), skin rash ($N=2$) and nausea ($N=1$) (300 mg, $N=3$; 250 mg, $N=1$; 200 mg, $N=4$). Regarding other established risk factors for CKD, 19 (23%) patients had obesity (using the definition for the Japanese population: body mass index > 25 kg/m^2 [17]), and 27 (33%) patients had a history of smoking. No patients had a family history of CKD.

Renal function

During the 5-year imatinib treatment, eGFR continuously decreased from 77 ± 17 to 62 ± 14 ml/min/1.73 m^2, and the change from baseline eGFR was significant ($P<0.001$,

Table 1 Patient characteristics at imatinib initiation ($N=82$)

Variables	
Median age, years [range]	49.5 [19–76]
Sex, *N*	
Male	60 (73%)
Female	22 (27%)
Previous interferon treatment, N	24 (29%)
Mean baseline estimated GFR (± SD), ml/min/1.73 m^2	77 ± 17
Comorbidities before treatment, N	
Hypertension	10 (12%)
Diabetes mellitus	6 (7%)
Chronic kidney disease[a]	12 (15%)
Obesity (body mass index ≥ 25 kg/m^2)	19 (23%)
History of smoking	27 (33%)
Median months of imatinib treatment [range]	105 [60–170]

[a]Defined by estimated GFR < 60 mL/min/1.73 m^2

GFR glomerular filtration rate

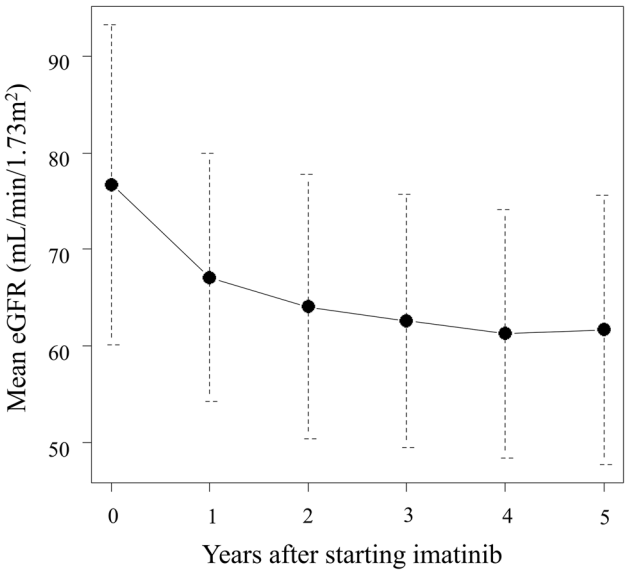

Fig. 1 Serial change of estimated glomerular filtration rate after starting imatinib. Analysis of the serial change of estimated glomerular filtration rate (eGFR) demonstrated a significant decrease over the 5-year imatinib treatment ($P<0.001$, repeated-measure ANOVA)

Table 2 Prevalence of chronic kidney disease before and after imatinib treatment ($N=82$)

CKD stages	Before imatinib treatment (*N*)	After 5-year imatinib treatment (*N*)
1	14	2
2	56	37
3	12	41[a]
4	0	2[a]
5	0	0

[a]Patients with higher stages significantly increased after treatment ($P<0.001$)

CKD chronic kidney disease

Fig. 1). The number of patients with eGFR less than 60 ml/min/1.73 m^2 was significantly increased to 43 (52.4%) patients from 12 (14.6%) at 5 years after initiating imatinib treatment ($P<0.001$). With respect to the CKD stages, the number of patients with higher stage CKD significantly increased after 5-year imatinib treatment (Table 2, $P<0.0001$). Spot disk urinalysis was performed in 13 patients, which detected trace and 1 + proteinuria in 6 and 2 patients, respectively. In the remaining 5 patients, proteinuria was not detected. At the timing of evaluation after treatment, only one patient had edema indicative of fluid collection. No patients presented heart failure. There was no significant difference in mean eGFR between patients treated with a decreased dose of imatinib ($N=8$) and those given a standard dose (400 mg/day, $N=74$) (50.8 ± 13.5 vs. 58.0 ± 13.7 ml/min/1.73 m^2, $P=0.16$). The blood concentration of imatinib was not measured in any of the patients because of the Japanese health insurance regulation. Of 82 patients, only three patients had been receiving angiotensin-converting enzyme-I inhibitor or angiotensin receptor blocker for hypertension. One of them developed CKD at 5 years after initiating imatinib.

The characteristics of the 70 patients without CKD upon imatinib initiation are shown in Table 3. Thirty-one patients developed CKD at 5 years after imatinib treatment. Age was significantly higher and baseline eGFR at initiating imatinib was significantly lower in patients who developed CKD after 5-year imatinib treatment compared with those who did not. On multivariate analysis, older age and lower eGFR at diagnosis were also identified as significant independent risk factors for developing CKD. Of 31 patients who developed CKD, 23 showed a more than 50% decline of the total eGFR decline of each patient in the first year (Fig. 2a). In contrast, eight patients showed a continuous or later-phase decline (Fig. 2b).

Relationship between hemoglobin level and renal function

The mean hemoglobin level at 5 years after starting imatinib was 12.4 ± 1.3 g/dl, which was significantly lower than that before starting imatinib (12.9 ± 1.7 g/dl, $P<0.01$). The median mean corpuscular volume was 98 fL (range 90–105) at 5 years after starting imatinib. At 5 years after starting imatinib, the rate of decrease in eGFR was negatively correlated with hemoglobin levels (correlation coefficient, -0.249, $P<0.05$; Fig. 3).

In 54 patients developing anemia, which was defined as a hemoglobin level of less than 13.5 g/dl for males and 11.5 g/dl for females, fecal occult blood was examined in 18, which was negative in all patients. The mean leukocyte and platelet counts at 5 years after initiating imatinib treatment were 4541 ± 1409/μL and $187.2\pm41.1\times10^9$/L, respectively, and the number of patients with the values less than the institutional normal ranges were 6 (11%) for leukocyte and 5 (9%) for platelet, respectively.

Thirty-six patients developed anemia concurrently with renal dysfunction (eGFR less than 60 ml/min/1.73 m^2) after 5-year imatinib treatment. In 16 of these patients, the serum erythropoietin (EPO) level had been measured, and the median serum EPO level was 32.7 mIU/ml (range 9.1–119). Despite the presence of anemia, the level EPO was higher than 100 mIU/ml only in one patient. Three patients developing moderate or progressive anemia (hemoglobin level of less than 10 g/dl) were treated with

Table 3 Characteristics of patients without chronic kidney disease (estimated GFR < 60 mL/min/1.73 m^2) at initiation of imatinib treatment

Variables	All patients	eGFR after 5-year imatinib		Univariate analysis	Multivariate analysis
		< 60 mL/min/1.73 m^2	≥ 60 mL/min/1.73 m^2		
	(*N* = 70)	(*N* = 31)	(*N* = 39)	*P*	*P*
Median age, years [range]	44 [19–76]	53 [35–76]	37 [19–63]	< 0.001	0.001
Sex, *N*					
Male	51	20	31	0.19	
Female	19	11	8		
Previous interferon, N	22	11	11	0.61	
Dose of imatinib, *N*					
≥ 400 mg/day	64	28	36	1.00	
< 400 mg/day	6	3	3		
Mean baseline eGFR, ml/min/1.73 m^2	81 ± 14[a]	74 ± 10[a]	85 ± 15[a]	0.002	0.008
Other factors before treatment, *N*					
Hypertension	8	4	4	1.00	
Diabetes mellitus	6	4	2	0.39	
Obesity (BMI ≥ 25 kg/m^2)	17	8	9	0.79	
History of smoking	26	14	12	0.32	

[a]Mean ± SD

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *BMI* body mass index

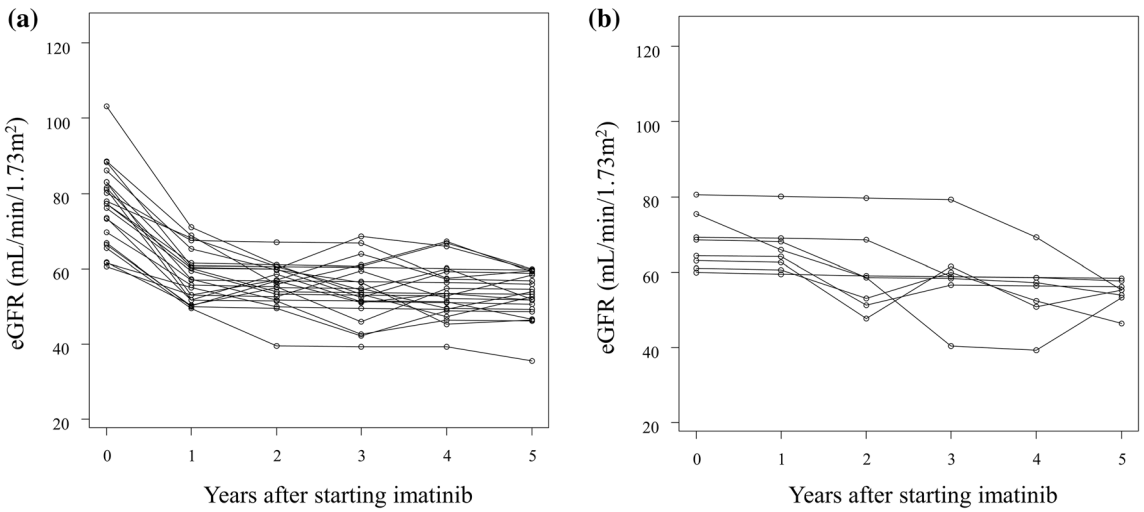

Fig. 2 Serial change of estimated glomerular filtration rate in patients without chronic kidney disease at initiating imatinib but developed CKD. **a** Twenty-three patients showed a more than 50% decline of total eGFR decline each patient in the first year. **b** Eight patients showed a continuous or later-phase decline

erythropoiesis-stimulating agents (ESA), and ESA increased the hemoglobin levels in all these patients. Especially, in one patient with an EPO level of 19.3 mIU/ml, requiring red cell transfusion, the hemoglobin level was increased to 11 g/dl from less than 7 g/dl by ESA administration.

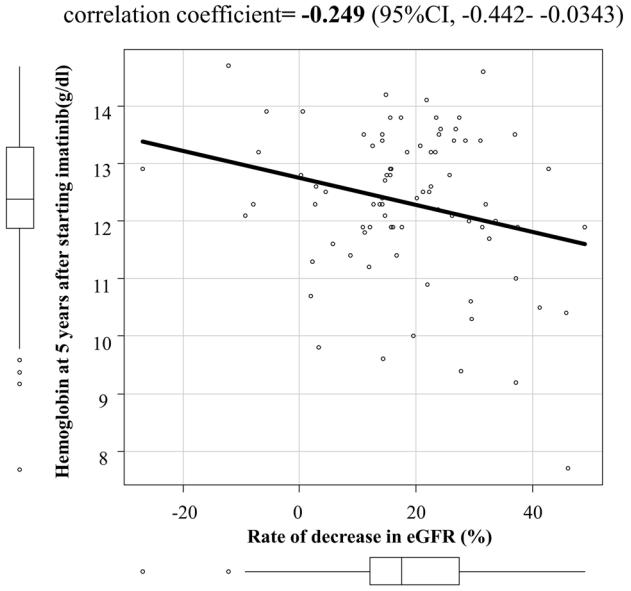

Fig. 3 Correlation between the decrease rate of the estimated glomerular filtration rate and hemoglobin levels after 5-year imatinib treatment. The rate of decrease of the estimated glomerular filtration rate (eGFR) was negatively correlated with hemoglobin levels at 5 years after stating imatinib ($P < 0.05$)

Effect of imatinib discontinuation on renal dysfunction and anemia

Eleven patients with eGFR < 60 ml/min/1.73 m^2 achieved a durable molecular remission, and participated in an institutional TKI discontinuation trial. At 1 year after discontinuing imatinib, their mean eGFR values increased significantly (50.0 ± 6.5 to 56.0 ± 10.2 ml/min/1.73 m^2, $P < 0.05$, Fig. 4a), as did their hemoglobin levels (12.0 ± 1.7 to 14.0 ± 1.6 g/dl, $P < 0.01$, Fig. 4b).

Discussion

This retrospective analysis demonstrated that eGFR was significantly decreased after 5-year imatinib treatment in patients with CML in CP (77 ± 17 to 62 ± 14 ml/min/1.73 m^2). The decline rate of eGFR was reported to be 0.36 ml/min/1.73 m^2 per year on average in Japanese general population [18]. Compared with the data in general population, the 5-year eGFR decline (15 ml/min/1.73 m^2) was considered notably higher. We also determined that older age and lower eGFR at the time of starting imatinib were the risk factors for developing renal dysfunction. In addition, the hemoglobin level was significantly decreased after 5-year imatinib administration, which was also significantly associated with the decrease in eGFR. In a proportion of evaluated patients, the serum EPO level was not responsively elevated, and ESA effectively improved anemia. These results suggest that anemia after a long-term imatinib treatment could be partly associated with insufficient EPO production due to the renal dysfunction.

Our extensive search of the English literature identified two reports focusing on renal dysfunction in CML patients treated with imatinib [9, 10]. Marcolino et al. conducted an observational study and evaluated 105 patients treated with imatinib as an initial TKI. eGFR after the end of follow-up (median, 4.5 years) was significantly lower than that before (94 ± 21 vs. 81 ± 22 ml/min/1.73 m^2, $P < 0.001$). Renal dysfunction was associated with older age and comorbidities such as hypertension and diabetes [9]. Yilmaz et al.

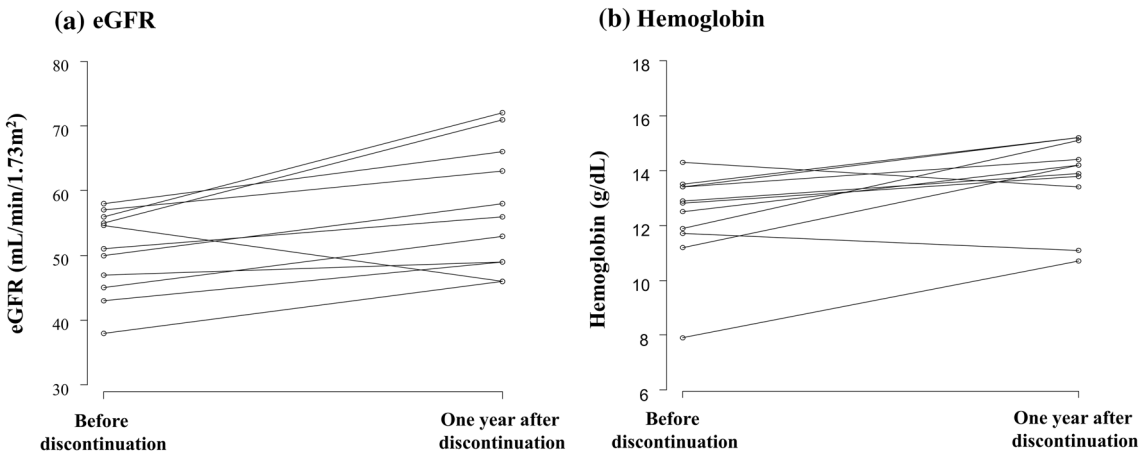

Fig. 4 Effect of imatinib discontinuation on the estimated glomerular filtration rate and hemoglobin level ($N = 11$). Eleven patients with renal dysfunction (eGFR less than 60 ml/min/1.73 m^2) achieved a durable molecular remission and joined an institutional TKI cessation study. Their mean eGFR values ($P < 0.01$) and mean hemoglobin levels ($P < 0.01$) were significantly increased at 1 year after discontinuation

retrospectively analyzed the data of 468 patients treated with TKIs, including imatinib, dasatinib and nilotinib, who had been enrolled into prospective clinical trials [10]. The choice of imatinib as TKI as well as a preexisting decrease in eGFR, age, and history of hypertension and diabetes were all significantly related to the development of renal dysfunction. Together with the consistent results of our present study, these findings strongly suggest that long-term use of imatinib is associated with a decline in eGFR levels in cooperation with other risk factors such as older age.

Regarding the anemia associated with imatinib treatment, the inhibitory effect of imatinib on hematopoietic stem/progenitor cells via c-kit should be considered as the possible mechanism [19]. There has been only one analysis of the development of anemia in imatinib treatment. That study enrolled 128 patients with CML after 3-year imatinib treatment [11], and found that 30% of patients had anemia (hemoglobin less than 12 g/dl), and 9% had hemoglobin less than 10 g/dl. All but 1 patient had normal serum creatinine levels according to age. As a treatment for anemia, two patients were treated with ESA, which improved anemia, although data on the serum EPO levels were not available. These findings could be partly explained by a possible inhibitory effect of imatinib on the proliferation of normal hematopoietic progenitor cells independent of c-kit signaling [20, 21]. Indeed, only a limited number of patients developing anemia after imatinib treatment showed leukocytopenia or thrombocytopenia in our study, which would appear to reinforce the findings of the earlier study. In addition, the results of our study demonstrated that the decline in eGFR was related to the development of anemia. Moreover, although the number of evaluated patients was limited, discontinuation of imatinib or initiation of ESA was effective in improving anemia. Although there have been studies showing the efficacy of ESA in improving anemia in patients receiving imatinib, those studies did not focus on the concurrent renal dysfunction [11, 22, 23]. Therefore, to the best of our knowledge, our present study is the first to show the possible relationship between renal dysfunction and anemia as part of the pathogenesis of imatinib-induced anemia. Together with these previous studies, our results strongly suggest that anemia due to long-term imatinib treatment is partly attributable to the renal dysfunction resulting in the impaired EPO production, whose pathogenesis is generally recognized as renal anemia. Renal anemia is more commonly observed in patients with impaired kidney function, especially when GFR falls below 60 ml/min/1.73 m^2 [24]. Although the pathogenesis of renal anemia is considered multifactorial, it has been suggested to be mainly due to absolute or relative decrease in EPO production. In the recent Kidney Disease Improving Global Outcomes guideline, ESA therapy is situationally recommended in CKD patients with hemoglobin less than 10.0 g/dl [25]. Therefore, ESA could be an optimal option for anemia observed under long-term imatinib treatment [22, 23].

Recently, several clinical trials demonstrated that TKIs could be discontinued in 30–50% of patients who had achieved a durable molecular remission [3–6]. In our study, eleven patients who indeed achieved a durable molecular complete remission joined an institutional TKI discontinuation trial [26] and succeeded in discontinuing imatinib. In these patients, eGFR values and hemoglobin levels were significantly improved at 1 year after discontinuation of imatinib. These findings reinforced the possible relationship between renal dysfunction and anemia associated with imatinib treatment, and further suggest that imatinib-induced late-onset nephrotoxicity and anemia are reversible, although possibly not completely. Although a further evaluation is required, our results suggest that successful discontinuation of imatinib has a favorable outcome on renal dysfunction and anemia.

The pathogenesis of nephrotoxicity due to imatinib treatment has not been fully elucidated. However, imatinib's inhibitory effect on platelet-derived growth factor receptors, which plays an important role in animal models of several nephropathies and in renal tubular regeneration after acute tubular necrosis, could be a possible explanation of imatinib nephrotoxicity [27–29]. Further studies are required to fully evaluate the pathogenesis of renal dysfunction of imatinib treatment.

The major limitations of this study were its retrospective nature and the limited number of evaluated subjects, particularly subjects with available serum EPO levels. Another limitation was that renal function was evaluated based only on eGFR. Therefore, future prospective studies enrolling more patients and evaluating renal function using more precise parameters—such as creatinine clearance and secretion, inulin clearance, and cystatin C—are warranted. The other limitation is the lack of pharmacokinetics data of imatinib, which should be incorporated into a future study.

In conclusion, our findings clearly indicated that long-term use of imatinib was frequently associated with continuous decline in renal function, which could lead to anemia partly due to impaired production of EPO. Although the degree of nephrotoxicity estimated by laboratory data is usually mild, close monitoring of renal function is recommended, particularly in older patients with pre-existing renal dysfunction. Large-scale prospective studies focusing on renal function, hemoglobin values, serum EPO and the efficacy of ESA treatment for anemia are required to further clarify the pathogenesis of imatinib-associated renal dysfunction and anemia.

Compliance with ethical standards

Conflict of interest SO and TM received research funding and honoraria for lectures from Bristol-Myers Squibb and Novartis Pharmaceuticals.

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