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ORIGINAL ARTICLE

Changes in estimated glomerular filtration rate in chronic myeloid leukemia patients treated front line with available TKIs and correlation with cardiovascular events

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Abstract

We investigated the median estimated glomerular filtration rate (eGFR) changes in chronic myeloid leukemia (CML) patients treated front line with tyrosine kinase inhibitors (TKIs). A large cohort of 397 patients—320 treated front line with imatinib, 25 with dasatinib, and 53 with nilotinib—was retrospectively analyzed at a single institution. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation for all patients at baseline and then at 6 and 12 months, and at the last follow-up. Taking into account eGFR changes during the first year of treatment and excluding other possible cardiovascular risk factors, we considered also the percentage of cardiovascular events in patients with modifications of this single parameter. Imatinib induced a decrease in median eGFR ($p = 0.01$): 42 patients treated with imatinib had a cardiovascular event, related to modification of eGFR, in the absence of other cardiovascular risk factors. In patients treated with nilotinib, the median eGFR did not decline from baseline: only 1 patient experienced an ischemic event, but the eGFR remained unchanged. In patients treated with dasatinib, the mean eGFR did not change significantly: 3 patients experienced a cardiac ischemic event, but in all patients the eGFR remained unchanged over time, while advanced age and metabolic alterations contributed to the ischemic events. This long-term follow-up has documented that imatinib may induce changes in the eGFR, which may contribute to the onset of ischemic events. Further analyses on larger series of CML patients are required to conclusively define the potential renal toxicity of second generation TKIs and the consequent risk of developing ischemic events.

Keywords Chronic myeloid leukemia · Estimated glomerular filtration · Cardiovascular events

Introduction

Tyrosine kinase inhibitors (TKIs) have drastically changed the outcome of patients with chronic myeloid leukemia (CML) and improved overall survival. Despite the improved efficacy reported with imatinib and then with second-generation TKIs used as frontline treatment, each drug exhibits a specific safety profile, mostly due to inhibition of off-target receptors [1]. There has been limited attention to the potential renal injury during long-term treatment with TKIs. Few published cases have indeed reported that imatinib may induce acute renal failure [2, 3] and different pathogenetic mechanisms have been suggested, including a tumor lysis syndrome effect or a direct toxic tubular damage. In particular, this latter effect could be due to direct cells exposition to metabolites derived from imatinib after glomerular filtration [4, 5]. The PDGF-R plays an important role in tubular cell regeneration [6, 7]. Imatinib may interfere with this pathway [8], while this appears to occur less with the second-generation TKIs dasatinib and nilotinib. So far, only two studies have reported the long-term effects of imatinib on kidney function [4, 5], both suggesting possible acute injuries in a low percentage of patients and a decreased estimated glomerular filtration rate (eGFR) over time. No further studies are available on the occurrence

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of chronic progressive renal failure in CML patients on long-term TKI treatment and on its potential association with the onset of cardiovascular events. The present study was designed to evaluate the incidence of chronic renal injury in a large cohort of CML patients treated front line in the real life outside of clinical trials with all available TKIs. We also evaluate the impact of eGFR changes over time on cardiovascular events associated to second-generation TKI therapy, in the absence of other well-known cardiovascular risk factors.

Patients and methods

Study group

We reviewed the medical charts of 397 chronic phase CML patients treated front line with a TKI at our Center between 2001 and 2016: 320 patients received imatinib, 24 dasatinib, and 53 nilotinib. All patients were diagnosed with Philadelphia chromosome positive or BCR-ABL positive CML and were followed at a single institution outside of clinical trials. The median period of observation is 9 years for imatinib and 2.5 years for second-generation TKIs. The starting dose of frontline imatinib was 400 mg once daily in 310 patients and 300 mg for the remaining 10 patients; dasatinib was given to all patients at 100 mg once daily and nilotinib at 300 mg twice daily. We excluded from the analysis patients with previous renal disturbances associated with an estimated GFR <60 ml/min/1.73 m^2 persisting for at least 3 months. Patients in accelerated or blast phase with an ECOG performance status score > 2 and with a New York Heart Association (NYHA) class 3–4 heart disease were also excluded from the analysis.

Follow-up

All patients were monitored according to the European LeukemiaNet recommendations, being checked every week for the first 3 months and then every 3 months. Medical records were reviewed to collect creatinine, urea, uric acid, and eGFR: the latter was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation performed better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less biases and greater accuracy. The CKD-EPI equation is:

$$\mathrm{GFR} = 141 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [9]. Chronic renal failure was defined as an estimated GFR <60 ml/min/1.73 m^2 persisting for at least 3 months [10]. The incidence of acute kidney injury (AKI) was also evaluated: it was defined as an increase in serum creatinine of ≥ 0.3 mg/dl [11]. Information about concomitant medications and all clinical events, with particular interest to cardiovascular events, were also collected. For imatinib-treated patients, eGFR was calculated until a switch to a second-generation TKI. The cardiovascular risk was assessed using the Systematic Coronary Risk Evaluation (SCORE Risk Charts) that takes into account gender, age, total cholesterol level, systolic blood pressure, and smoking status, and stratifies patients into low-, intermediate-, and high-risk categories. The SCORE risk was retrospectively calculated only for patients who developed a cardiovascular event during TKI treatment.

Statistical analysis

Statistical analysis was performed by using the Wilcoxon paired nonparametric test, which was used to detect the difference between baseline 6, 12 months, and final measurement of eGFR. A significance level of 0.05 was considered. We used the R statistical software version 3.3.3 for all analyses. Furthermore, for each study group, eGFR data were depicted by spaghetti plots where subject's measurements are reported longitudinally over time points.

Results

Patients

We evaluated 320 patients treated front line with imatinib, 25 with dasatinib, and 53 with nilotinib. In the imatinib cohort, the median period of observation is 9 years (range 0.8–14.8); 55.5% were males and 45.5% females, median age was 57.7 years (range 18.6–88.4), and the type of transcript at diagnosis was b3a2 in 209 (65.2%) patients, b2a2 in 105 patients (32.7%), and b3a2 + b2a2 in 6 (2.1%) patients. According to the Sokal score, 48.1% of patients were classified as low risk, 40% as intermediate, and 11.9% as high risk, whereas according to the ELTS score, 71.1% of patients were stratified as low risk, while 22.7 and 6.2% were categorized as intermediate risk and high risk, respectively. The EUTOS score identified 311 (97.1%) patients as low risk and 9 (2.9%) as high risk, while the Hasford score categorized 199 (62.2%) patients as low risk, 105 (32.7%) as intermediate, and 16 (5.1%) as high risk. Evaluation of the impact of comorbidities at baseline according to the Charlson comorbidity index at baseline revealed that 182 patients (56.8%) had a 0–2 score, 101 patients (32.5%) a 3 score, and the remaining patients

(11.5%) a 4–5 score. At baseline, the mean creatinine level was 0.9 mg/dL and the mean eGFR 81 ml/min for patients treated with imatinib (Table 1).

In patients treated front line with second-generation TKIs, the median observation time was 2.5 years (range 1.8–6). In this subset of patients, males were 42 (53.2) and females were 36 (46.2), median age was 52 years (range 20.4–84.5), and the type of transcript at diagnosis was b3a2 in 52 (66.6%) patients, b2a2 in 23 patients (29.5%), and b3a2 + b2a2 in 3 (3.9%) patients. The Sokal score identified 43 (55.1%) patients as low risk, 27 (34.6%) as intermediate risk, and 8 (10.3%) as high risk, while the Hasford score categorized 46 (58.9%) patients as low risk, 27 (34.7%) as intermediate, and 5 (6.4%) as high risk. According to the EUTOS score, 71 patients (91.1%) were classified as low risk and 7 (8.1%) as high risk, whereas according to ELTS, 61 (78.2%) were stratified as low risk, 14 (17.9%) as intermediate risk, and 3 (3.9%) as high risk. The Charlson comorbidity index at baseline revealed that 47 patients (60.2%) had a 0–2 score, 26 patients (33.3%) had a 3 score and 5 patients (6.5%) a score > 4. At baseline, the mean creatinine level was 0.7 mg/dL and the mean eGFR 98 and 93 ml/min for patients treated with nilotinib and dasatinib, respectively (Table 2).

Table 1 Baseline characteristics of patients treated with imatinib

N patients	320
Median age (range)	57.7 (18.6–88.4)
Sex M/F (%)	174 (55.5)/146 (45.5)
Type of transcript	
B3a2 (%)	209 (65.2)
B2a2 (%)	105 (32.7)
B3a2 + B2a2 (%)	6 (2.1)
Eutos score	
Low (%)	311 (97.1)
High (%)	9 (2.9)
Hasford score	
Low (%)	199 (62.2)
Intermediate (%)	105 (32.7)
High (%)	16 (5.1)
Sokal score	
Low (%)	154 (48.1)
Intermediate (%)	128 (40)
High(%)	38 (11.9)
Eutos long-term survival (ELTS)	
High (%)	228 (71.1)
Intermediate (%)	73 (22.7)
High (%)	19 (6.2)
Charlson comorbidity index (CCI)	
Score 0–2 (%)	182 (56.8%)
Score 3 (%)	101 (32.5)
Score 4–5 (%)	37 (11.5)
Starting dose of imatinib	
400 mg/die	310 (96.8%)
300 mg/die	10 (3.2%)
Mean creatinine level at baseline (mg/dl)	0.9
Mean eGFR level at baseline (ml/min)	81
Median follow-up (years)	9 (0.8–14.8)

Renal function changes and cardiovascular disease related to eGFR modifications

Imatinib induced a decrease in median eGFR from 81 ml/min at baseline, to 78 ml/min at 6 months, 77 ml/min at 12 months, and 71 ml/min at the last follow-up ($p = 0.01$) (Table 3; Fig. 1). The mean eGFR decrease in the first year of treatment was

Table 2 Baseline characteristics of patients treated with second generation TKIs

N patients	78
Median age (range)	52 (20.4–84.5)
Sex M/F (%)	42 (53.2)/36 (46.2)
Type of transcript	
B3a2 (%)	52 (66.6)
B2a2 (%)	23 (29.5)
B3a2 + B2a2 (%)	3 (3.9)
Eutos score	
Low (%)	71 (91.1)
High (%)	7 (8.9)
Hasford score	
Low (%)	46 (58.9)
Intermediate (%)	27 (34.7)
High (%)	5 (6.4)
Sokal score	
Low (%)	43 (55.1)
Intermediate (%)	27 (34.6)
High (%)	8 (10.3)
Eutos long-term survival (ELTS)	
Low (%)	61 (78.2)
Intermediate (%)	14 (17.9)
High (%)	3 (3.9)
Charlson comorbidity index (CCI)	
Score 0–2 (%)	47 (60.2)
Score 3 (%)	26 (33.3)
Score 4–5 (%)	5 (6.5)
Starting dose of nilotinib and dasatinib	
600 mg/die	53 (100)
100 mg/die	25 (100)
Mean creatinine level at baseline (mg/dl)	0.7
Mean eGFR level at baseline (ml/min) in nilotinib group	98
Mean eGFR level at baseline (ml/min) in dasatinib group	93
Median follow-up (months)	2.5 (1.8–6)

Table 3 eGFR changes at several time-points according to the TKI treatment

Number of pts* (*N*)	Tki** therapy	Mean decreasing of eGFR*** after 12 months of therapy (ml/min)	Median eGFR*** at baseline (ml/min)	Median eGFR*** at 6 months (ml/min)	Median eGFR*** at 12 months (ml/min)	Median eGFR*** at last follow-up (ml/min)	*p* value
320	Imatinib	3	81	78	77	71	0.01
53	Nilotinib	/	98	107	94	92	0.11
24	Dasatinib	6	93	83	81	80	0.167

*Patients

**Tyrosine kinase inhibitor

***Estimated glomerular filtration rate

3 ml/min. Thirteen patients (4%) developed an imatinib-associated acute kidney injury (AKI) during the first 12 months of treatment with a median time from start of the TKI to the first onset of AKI of 12 days (range 3–73). No patient had to discontinue or switch TKI due to AKI. All patients who developed AKI were receiving imatinib at 400 mg daily dose. We also analyzed whether the eGFR change was different in patients who were treated with a reduced dose of imatinib (300 mg daily): the decreasing tendency of the eGFR was observed also in this small group of patients with no difference compared to patients who received 400 mg daily of imatinib ($p = 0.431$). Forty-two patients treated with imatinib had a cardiovascular event: the evaluation of cardiovascular risk factors in these patients according to the SCORE chart showed that 55.1% were low risk, 35.3% intermediate risk, and 9.6% high risk. In these patients, the median eGFR decreased from 75 ml/min at baseline to 67 ml/min at the last follow-up ($p = 0.04$) with a mean decrease of eGFR of 3 ml/min in the first year of treatment. Fourteen of the 42 patients (median age 57 years, range 45–88) had a myocardial infarction that required hospitalization: 10 patients had a low SCORE chart classification and 4 patients an intermediate risk (Table 4). eGFR modifications seem to be the reason of these events in the absence of worsening of other concomitant cardiovascular risk factors.

In patients treated with nilotinib, the eGFR did not decline from baseline, starting from 98 ml/min at baseline and becoming 107 ml/min at 6 months, 94 ml/min at 12 months, and 92 ml/min at the last follow-up ($p = 0.11$) (Table 3; Fig. 1). Interestingly, mean eGFR increased in patients treated with nilotinib during the first 6 months of treatment. The mean increase from baseline was 6 ml/min after 6 months of therapy. No patient developed a nilotinib-associated AKI during the first 12 months of treatment. Only one patient experienced

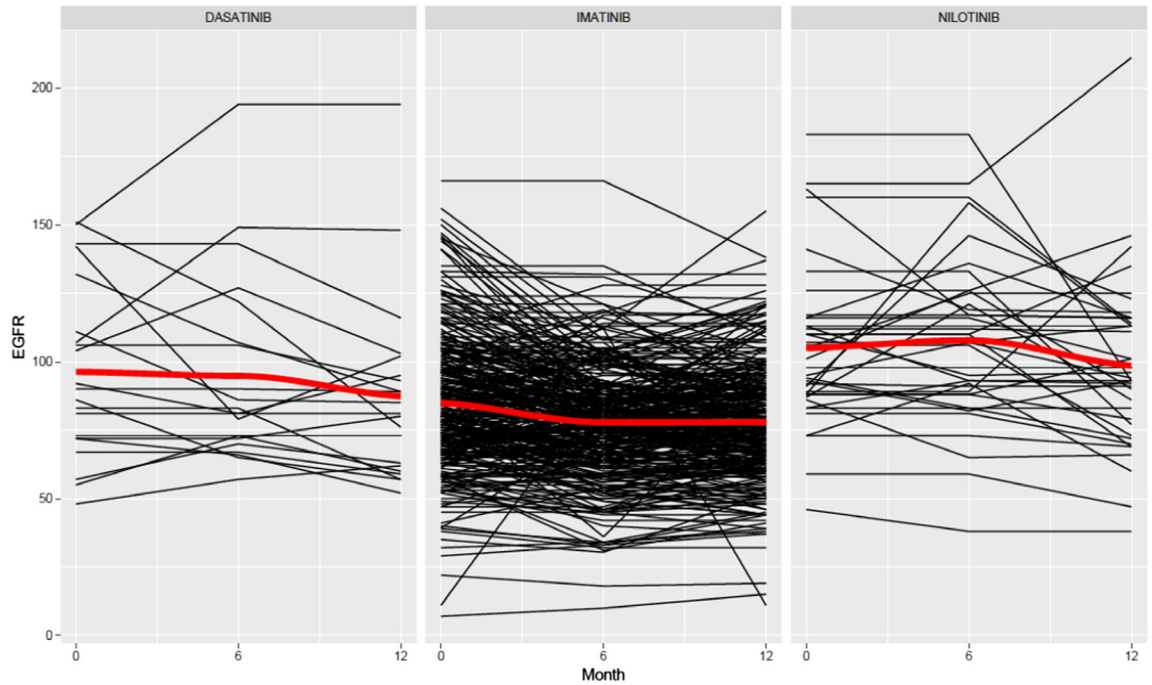

Fig. 1 eGFR changes at several time-points according to the TKI treatment

an ischemic event, but the eGFR remained unchanged. Furthermore, the patient had a high risk of cardiovascular events according to the SCORE chart classification (Table 4).

In patients treated with dasatinib, the mean eGFR started from 93 ml/min then declined to 83 ml/min at 6 months, to 81 ml/min at 12 months, and to 80 ml/min at the last follow-up ($p = 0.167$) (Table 3; Fig. 1). The mean decrease of the eGFR during the first year of treatment was 6 ml/min. In this subset of patients, we observed an AKI in 1 patient (4%) during the first 12 months of treatment. Even if a decline was noted, statistical significance was not reached due to the small series of patients analyzed. Three patients experienced a cardiac ischemic event, but in no patient the eGFR changed over time, while advanced age and metabolic alterations contributed to the ischemic event. Indeed, 1 of these patients had a high SCORE chart classification, while 2 patients had an intermediate risk (Table 4).

Discussion

CML patients are expected to receive treatment with TKIs for a prolonged time period. The main focus in the management of CML patients over the last years has been to identify and manage the long-term potential consequences and toxicities due to prolonged exposure to these drugs. Our study focused on the potential worsening of renal function during TKI treatment comparing patients who received imatinib or second-generation TKIs as frontline treatment and the possible correlation with the occurrence of cardiovascular events, in the absence of worsening of other risk factors. We evaluated the kidney function at several time-points by using the CDK-EPI creatinine equation that through a specific formula has been proven more accurate than the Modified of Diet in Renal Disease (MDRD) study equation routinely used in the common clinical practice [9]. As monitoring of serum creatinine is not a sensitive estimator of kidney function, this latter equation represented a crucial tool in evaluating the eGFR and should be always considered especially in patients who receive prolonged TKI treatment. Our analysis suggests that patients who received imatinib showed a significant decline of the eGFR ($p = 0.01$) over time compared to those who received a second generation TKI. Furthermore, imatinib resulted the only TKI associated with development of AKI. However, the imatinib group consisted of a much greater number of patients analyzed (320 vs 78), a longer median period of observation (9 years vs 2.5 years), a greater median age at diagnosis (57.7 vs 52) and a higher percentage of patients who presented a score 4–5 of CCI at baseline (11.5 vs 6.5) compared to the dasatinib/nilotinib group. All the above may associate with a higher probability of an eGFR worsening during the follow-up period and, in particular, the upper age and the presence of more comorbidities in the imatinib group might result in a greater risk of developing nephropathies. We also noted that in the imatinib group all 42 patients who developed a cardiovascular event showed a worsening of the eGFR, with a significant median decreasing of its value from the baseline to the last follow-up ($p = 0.04$). Interestingly, among the 14 patients who had a myocardial infarction, none presented a high cardiovascular risk according to the SCORE chart. These latter results, may suggest that eGFR could represent an independent predictive factor in developing cardiovascular events and should be always taken into account in patients treated with TKIs, especially in those who already presented others risk factors at baseline. The progressive worsening of the eGFR in this subset of patients should be considered as a warning not only for the potential occurrence of a chronic kidney failure, but also for an increased risk of cardiovascular events. Moreover, also in the dasatinib group we observed a progressive worsening trend of the eGFR

Table 4 Cardiovascular events and correlation with eGFR changes according to the TKI treatment

TKI** therapy	Cardiovascular events *n* (%)	SCORE***** chart classification of patients developing cardiovascular events *n* (%)	Median eGFR*** at baseline (ml/min) in pts* with cardiovascular events	Median eGFR*** at last follow-up (ml/min) in pts* with cardiovascular events	*p* value
Imatinib	42 (13.1%)	Low risk 23 (55.1%) Intermediate risk 15 (35.3%) High risk 4 (9.6%)	75	64	0.04
Nilotinib	1 (1.8%)	Low risk 0 (0%) Intermediate risk 0 (0%) High risk 1 (100%)	102	99	NS
Dasatinib	3 (12.5%)	Low risk 0 Intermediate risk 2 (66.6%) High risk 1 (33.4%)	90	87	NS

*Patients

**Tyrosine kinase inhibitor

***Estimated glomerular filtration rate

****Systematic Coronary Risk Evaluation

during the period of treatment analyzed, but, overall, the total change did not result significant, probably due to the small cohort of patients analyzed. Interestingly, nilotinib was the only TKI associated with an increase of the eGFR. The exact pathogenetic mechanism(s) underlying kidney functional changes induced by TKIs are still unclear. The capability of TKIs to inhibit PDGFR-α and PDGFR-β receptors, especially mediated by imatinib, could represent one of the renal impairment causes. In an animal model (rat), it has been reported that imatinib, by inhibiting the PDGFR receptor, may induce alterations of tubulogenesis and tubules repair after a renal-perfusion injury [6, 7, 12]. However, in all other animal models tested, the inhibition of PDGF after an injury has been associated with an improvement of the renal function. PDGF seems to play a crucial role in stimulating the extracellular matrix synthesis and the mesangial cell proliferation that may promote kidney damage with a subsequent occurrence of nephropathies [13–15]. Several studies reported that the renal function in animal models affected by nephropathies such as lupus nephritis or diabetic nephropathy [16] may improve after TKI therapy [14]. These latter data may explain the improvement of the eGFR in the first 6 months of treatment observed in the nilotini-treated patients. In conclusion, the eGFR, evaluated with the CDK-EPI creatinine equation, should be persistently monitored during all the course of treatment. We documented that imatinib may induce significant changes in eGFR over time. We also noted that, in some patients, the changes of eGFR might potentially be correlated with the occurrence of ischemic events in the absence of other concomitant cardiovascular risk factors, but further analyses are required to confirm this potential association. In this light, it is important to consider individualizing the treatment for each single patient, considering the concomitant cardiovascular risk factors, the concomitant comorbidity profile, and the potential off-target effects of the available TKIs.

Authors' contribution MB designed the study and wrote the manuscript; MM collected data and wrote the manuscript; DAF analyzed data; ES, MC, GC, FM, and RL followed patients; and RF critically revised the paper and approved the final version.

Compliance with ethical standards

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

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