Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients

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Background: We analyzed the incidence of acute kidney injury and chronic renal failure in chronic myeloid leukemia (CML) patients using imatinib and investigated whether there is a relation between duration of imatinib therapy and decrease in estimated glomerular filtration rate (GFR).

Patients and methods: One hundred five CML patients on imatinib therapy were enrolled. Creatinine, urea, uric acid, and potassium measurements from imatinib treatment onset until the end of follow-up (median 4.5 years) were included in the analysis. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Results: During follow-up, 7% of patients developed acute kidney injury; creatinine levels returned to baseline in only one of them. According to the regression equation, the mean baseline value of the estimated GFR was 88.9 ml/min/1.73 m². Estimated GFR decreased significantly with imatinib treatment duration; the mean decrease per year was 2.77 ml/min/1.73 m² (P < 0.001); 12% of patients developed chronic renal failure. Age, hypertension, and a history of chronic renal failure or interferon usage were not significantly related to the mean decrease in the estimated GFR over time.

Conclusion: The introduction of imatinib therapy in nonclinical trial CML patients is associated with potentially irreversible acute renal injury, and the long-term treatment may cause a clinically relevant decrease in the estimated GFR.

Key words: acute kidney injury, adverse effects, chronic renal failure, drug-induced nephrotoxicity, imatinib, protein kinase inhibitors

Introduction

Imatinib mesylate was the first tyrosine kinase inhibitor to be successfully used in clinical practice. It represents a prototype of therapeutic agents that are characterized by target specificity and optimal therapeutic index [1]. Its introduction has revolutionized the management of chronic myeloid leukemia (CML) and advanced gastrointestinal stromal tumors. Imatinib is not only more effective in delaying disease progression and improving survival time but is also associated with fewer adverse effects compared with traditional chemotherapy, including interferon (IFN) and busulfan. Therefore, it has become the first-line treatment of these diseases [2, 3].

Although the efficacy and tolerability of imatinib represents a major improvement over conventional chemotherapies, the drug exhibits off-target effects. Imatinib was designed to specifically target BCR–ABL, a protein with autonomous tyrosine kinase activity, originated from the BCR-ABL fusion gene, which was formed by the juxtaposition of a portion of the human homolog of the Abelson murine leukemia (ABL) gene from chromosome 9 and the breakpoint cluster region (BCR) gene of chromosome 22. Many off-target kinases, however, are also affected [4]. A number of case reports suggest that imatinib may be associated with acute renal failure [5–10]. Some authors suggested that this adverse effect may be caused by two possible mechanisms: tumor lysis syndrome, with precipitation and deposition of uric acid in the renal tubules, and toxic tubular damage. Tubular cells are susceptible to the toxic effects of drugs, as they have a role in concentrating and reabsorbing the glomerular filtrate, what exposes them to high levels of circulating toxins [11]. In the case of imatinib, the toxic effect may be related to platelet-derived growth factor receptor (PDGFR) inhibition [12]. Platelet-derived growth factor β-chain (PDGF-β) expression has been reported in proximal tubules and mesangial and interstitial cells [13]. It has been shown in animal models that PDGFR-β/PDGFR axis plays an important role in renal tubular cell regeneration after acute tubular necrosis [14]. So, by inhibiting PDGFR, imatinib may interfere in tubular repair mechanisms.

Trials in chronic phase CML patients have not reported any case of acute renal failure as an adverse effect of imatinib [15, 16]. A phase I study in blast crisis CML and acute
lymphoblastic leukemia patients reported just one case (1.7%) of acute renal failure probably related to imatinib [17]. However, patients with creatinine >1.5 times the institutional upper limit of normal were excluded from these trials. Considering that CML is more common in elderly people, with a median age at diagnosis of ~65 years, and that the prevalence of decreased glomerular filtration rate (GFR; <90 ml/min/1.73 m^2, as defined by the National Kidney Foundation) can be as high as 60% in 60- to 69-year-old individuals and even 74% in older individuals [18, 19], the exact incidence of this adverse effect in nonclinical trial patients is still uncertain. Additionally, there is lack of evidence regarding the effect of long-term imatinib treatment on renal function and the occurrence of chronic progressive renal failure in these patients.

The present study was designed to overcome this limitation. Our objective was to assess the incidence of acute kidney injury and chronic renal failure in CML patients using imatinib without a particular selection of renal function or age at study entry. Another objective was to elucidate whether there is a relation between duration of imatinib therapy and decrease in estimated GFR.

patients and methods
study design and patient selection
This observational study enrolled 105 CML patients receiving imatinib therapy who were included in a study by Ribeiro et al. [20] to assess imatinib cardiotoxicity. In that study, there were 103 patients using imatinib, but some control patients also started the imatinib therapy during follow-up and were included in this study.

Patients were recruited at the outpatient clinic of the Hematology Service of the Universidade Federal de Minas Gerais (UFMG), Brazil, an academic tertiary referral hospital. Confirmation of diagnosis was obtained by either the Philadelphia chromosome identification or the BCR-ABL transcripts, or both, in peripheral blood or bone marrow cells. Eligible patients were at least 18 years old. Exclusion criteria were any kind of established heart disease (valvular or congenital heart disease, heart failure, pacemaker usage, and history suggestive of coronary heart disease or arrhythmias), resistant arterial hypertension (blood pressure that remained above target levels in spite of the concurrent use of three antihypertensive agents of different classes at optimal doses) [21], significant anemia (hemoglobin <9 g/dl), chronic obstructive pulmonary disease (suggested by clinical signs, symptoms, risk factors, and radiological alterations or confirmed by spirometry), and history of alcohol or substance abuse or dependence (Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition criteria), as reported previously [20]. Renal disturbances were not considered to be exclusion criteria in this study.

The study was approved by the institutional review board of UFMG, and all patients gave written informed consent.

imatinib treatment and data collection
According to the country heath policy and our institution protocol at the time these patients were diagnosed, all patients received initial treatment with a xanthine oxidase inhibitor and hyperhydration, regardless of the peripheral white blood cell (WBC) count or uric acid concentration at diagnosis. Unless WBC counts were <20 x 10^9/L, patients also received cytoreductive therapy (hydroxyurea) before initiation of CML treatment with IFN-α or imatinib. IFN-α was initiated in chronic phase CML patients. Imatinib was initiated in cases of accelerated disease or blast crises and, in chronic phase disease, in cases of relapsed or refractory CML or in patients who were unable to tolerate IFN.

imatinib dose was at the discretion of the treating physician (hematologist) and was not specified in the research protocol (observational study). Patient compliance was verified at each appointment and also monthly in pharmacy records, as part of patient care. A case report form was developed to collect data regarding the use of imatinib and concomitant use of other drugs.

Medical records were reviewed to collect creatinine, urea, uric acid, and potassium measurements. All laboratory measurements of these parameters from the start of imatinib treatment were recorded for all patients. Information about co-medication and clinical events that might be responsible for creatinine changes was also collected.

end point definitions
The primary end point outcomes were creatinine and estimated GFR. Although creatinine is not a sensitive method to estimate the renal function (>40% of renal function has to be affected before it is able to detect decreases in GFR) [22], there is accumulating evidence that small increments in serum creatinine are associated with short- and long-term adverse outcomes [23]. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation, which was shown to be more precise and accurate than the Modification of Diet in Renal Disease Study equation, especially at estimated GFRs ≥60 ml/min/1.73 m^2 [24].

The primary clinical outcomes were acute kidney injury and chronic renal failure. In this study, acute kidney injury was defined as an increase in serum creatinine of 20.3 mg/dl or a percentage increase in serum creatinine of ≥50% when comparing the serum level before and the first one after the start of imatinib treatment. Although small increments in serum creatinine are often attributed to laboratory variations, 0.3 mg/dl increments are unlikely to be due to this variation [23]. Chronic renal failure was defined as an estimated GFR <60 ml/min/1.73 m^2 persisting for at least 3 months. This outcome was measured only among patients with an estimated GFR of at least 60 ml/min at baseline [22, 25].

statistical analysis
The statistical analysis was carried out using SAS (SAS Institute, Cary, NC) version 9.2 and SPSS statistical software (SPSS Inc., Chicago, IL) release 17.0. Distributions of data were examined for normality by using Kolmogorov–Smirnov tests. Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Categorical variables were expressed as counts and percentages.

To investigate the hypothesis that creatinine and estimated GFR might be related to imatinib treatment duration, subject-level linear regression analysis was carried out. The linear regression of estimated GFR on treatment duration was determined for each patient and was summarized by patient-based intercepts and slopes. We report mean values and SDs for both statistics. Unpaired t-test was used to compare the differences in baseline estimated GFR and slope according to demographic and clinical characteristics. The clinical characteristics were chosen based on prior research of their relationship with nephropathy and/or creatinine levels (age, hypertension, diabetes, chronic renal failure at baseline, and previous IFN treatment).

A P value of 0.05 was considered statistically significant and all P values are two-tailed.

results
patients
This study enrolled 105 patients, 100 (95%) of whom were in chronic phase CML, 4 (4%) in accelerated phase, and 1 patient in blast crisis. Seven patients were receiving imatinib for CML relapse after allogeneic stem-cell transplantation. The prognostic score of Sokal [26] was determined in 84 (80%)
patients at the time of diagnosis; it was not available for some patients who were referred from outside centers. The mean value was 0.9 (IQR 0.7–1.3, ranging from 0.5 to 4.3).

The median duration of imatinib treatment was 4.5 (IQR 3.2–6.1) years. The observed rate of complete hematologic response (defined as WBC <10 × 109/l; basophils <5%; absence of myelocytes, promyelocytes, or myeloblasts in the differential count; platelet count <450 × 109/l; nonpalpable spleen) was 98%, major cytogenetic response was 93% (0%–35% Philadelphia chromosome-positive (Ph+) metaphases), and complete cytogenetic response was 84% (no Ph+ metaphases). Eighteen percent of the patients had complete molecular response (undetectable BCR–ABL messenger RNA transcripts by real-time quantitative PCR in two consecutive blood samples of adequate quality) and 54% had major molecular response (ratio of quantitative PCR in two consecutive blood samples of adequate quality) and 54% had major molecular response (ratio of BCR–ABL to ABL <0.1% on the international scale).

Previous use of hydroxyurea was reported in 102 patients (97%) and of IFN in 77 patients (76%); median IFN treatment time was 5 months (ranging from less than 1 full month to 5.2 years, IQR 1–15 months).

Clinical features are summarized in Table 1.

**renal function**

During follow-up, seven patients (7%) developed acute kidney injury according to the study definitions. Clinical characteristics of these patients are described in Table 2. Uric acid and potassium concentrations remained below the levels considered diagnostic for tumor lysis syndrome [27]. None of these patients had chronic renal failure at baseline, although one patient (a 23-year-old male) had a diagnosis of membranous glomerulonephritis related to CML. All of them were previously treated with IFN-α. Creatinine levels returned to baseline in only one patient, and one patient developed chronic renal failure.

Among patients who did not have chronic renal failure at baseline (n = 100), 16 (16%) developed chronic renal failure, in this study defined as an estimated GFR ≤60 ml/min/1.73 m² persisting for at least 3 months. When compared with patients who did not develop renal failure, these patients were older and had a higher frequency of hypertension and diabetes (Table 3). In 12 of these patients (75%), the estimated GFR did not return to levels >60 ml/min/1.73 m² at any time during follow-up. Most of these patients were 60 years or older (83%) and had arterial hypertension (67%) (Table 4). Six patients were using an angiotensin-converting enzyme (ACE) inhibitor to treat hypertension, but in only one of them it was started after imatinib treatment onset. However, chronic renal failure developed in this patient before the introduction of the ACE inhibitor. He had also a history of occasional nonsteroidal anti-inflammatory drug usage to alleviate joint pain. No other patients had a history of use of anti-inflammatory drugs.

When analyzing separately the four patients who developed chronic renal failure without a history of hypertension or diabetes, we found that three of the four patients were older than 60 years of age at imatinib treatment onset, had a baseline estimated GFR <70 ml/min/1.73 m², and received a mean daily dose of 400 mg of imatinib. One patient, who was young (46 years old), had a baseline estimated GFR of 88 ml/min/1.73 m² and was treated with imatinib 600 mg/day for accelerated phase CML. All these patients had been previously treated with hydroxyurea and three had also received IFN as first-line treatment. None of them underwent hematopoietic stem-cell transplantation.

Estimated GFR decreased significantly with imatinib treatment duration. The mean estimated GFR was 94 ± 21 ml/min/1.73 m² at baseline and 81 ± 22 ml/min/1.73 m² at the last follow-up measure (P < 0.001).

The mean baseline value of the estimated GFR that is based on the individual regression equations for the entire cohort was 88.9 ml/min/1.73 m² (i.e. the mean value of the intercepts) and the mean decrease per year (i.e. the mean value of the slopes)

**Table 1.** Baseline characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>HT</th>
<th>DM</th>
<th>Uric acid(a) (mg/dl)</th>
<th>Baseline eGFR (ml/min/1.73 m²)</th>
<th>eGFR after IM (ml/min/1.73 m²)</th>
<th>Time interval(b) (days)</th>
<th>Lowest eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>M</td>
<td>−</td>
<td>−</td>
<td>5.2</td>
<td>133</td>
<td>105</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>37</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>4.6</td>
<td>124</td>
<td>94</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>−</td>
<td>−</td>
<td>5.6</td>
<td>103</td>
<td>69</td>
<td>28</td>
<td>69</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>4.1</td>
<td>129</td>
<td>90</td>
<td>14</td>
<td>90</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>+</td>
<td>−</td>
<td>5.7</td>
<td>104</td>
<td>77</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>3.7</td>
<td>147</td>
<td>104</td>
<td>37</td>
<td>86</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>5.1</td>
<td>93</td>
<td>60</td>
<td>27</td>
<td>52</td>
</tr>
</tbody>
</table>

(a)First measure after imatinib treatment onset. Normal range is 2.5–6.2 mg/dl for women and 3.5–8.5 mg/dl for men.

(b)Time interval between imatinib treatment onset and first creatinine measure.

HT, hypertension; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IM, imatinib treatment onset; M, male; F, female.
was 2.77 ml/min/1.73 m$^2$ ($P < 0.001$). Age, hypertension, and a history of chronic renal failure were significantly related to the mean baseline estimated GFR (Table 5), but no variable was significantly related to the mean decrease in the estimated GFR over time (Table 6). The variation of estimated GFR over time in patients without and with impaired renal function at baseline is illustrated in Figures 1 and 2, respectively.

Subsequently, we compared the mean decrease in the estimated GFR per year observed in the present study with the decrease in creatinine clearance observed in healthy volunteers in the Baltimore Longitudinal Study (0.75 ml/min/1.73 m$^2$/year), and they were significantly different ($P < 0.001$). The mean decrease in estimated GFR observed in the present study was also significantly different from a group of individuals of the Baltimore Longitudinal Study taking antihypertensives and/or diuretics (0.92 ml/min/1.73 m$^2$/year, $P < 0.001$) [28].

discussion

This study suggests that the introduction of imatinib therapy in nonclinical trial CML patients is associated with acute renal injury, which is most often irreversible, and that the long-term treatment is related to a clinically relevant decrease in the estimated GFR that may lead to chronic renal failure.

Table 3. Clinical characteristics of patients who developed chronic renal failure at any time during follow-up versus patients who did not develop chronic renal failure

<table>
<thead>
<tr>
<th></th>
<th>CRF (n = 16)</th>
<th>No CRF (n = 84)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (52–72)</td>
<td>42 (31–50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>8 (50)</td>
<td>40 (48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (63)</td>
<td>16 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (19)</td>
<td>3 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>3 (19)</td>
<td>6 (8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous IFN</td>
<td>14 (88)</td>
<td>64 (76)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or number (%). CRF, chronic renal failure; IFN, interferon-α.

Table 4. Clinical and laboratory characteristics of patients who developed chronic renal failure during follow-up

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>HT</th>
<th>DM</th>
<th>Uric acid (mg/dl)</th>
<th>Baseline eGFR (ml/min/1.73 m$^2$)</th>
<th>Last eGFR (ml/min/1.73 m$^2$)</th>
<th>Acute kidney injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>5.2</td>
<td>88</td>
<td>47</td>
<td>−</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>5.1</td>
<td>93</td>
<td>60</td>
<td>−</td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>NA</td>
<td>64</td>
<td>42</td>
<td>−</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>+</td>
<td>−</td>
<td>3.0</td>
<td>73</td>
<td>55</td>
<td>−</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>69</td>
<td>37</td>
<td>−</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>−</td>
<td>−</td>
<td>3.7</td>
<td>67</td>
<td>50</td>
<td>−</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>68</td>
<td>32</td>
<td>−</td>
</tr>
<tr>
<td>67</td>
<td>F</td>
<td>+</td>
<td>−</td>
<td>3.0</td>
<td>77</td>
<td>56</td>
<td>−</td>
</tr>
<tr>
<td>82</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>4.9</td>
<td>81</td>
<td>49</td>
<td>−</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>+</td>
<td>−</td>
<td>7.1</td>
<td>68</td>
<td>49</td>
<td>−</td>
</tr>
<tr>
<td>76</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>6.1</td>
<td>63</td>
<td>29</td>
<td>−</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>−</td>
<td>−</td>
<td>4.8</td>
<td>61</td>
<td>50</td>
<td>−</td>
</tr>
</tbody>
</table>

HT, hypertension; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; M, male; NA, not available.

To our knowledge, this is the first study that evaluated the renal function in patients receiving long-term imatinib treatment. Evaluation of the long-term effects of imatinib exposure is essential, as the optimal duration of therapy in CML patients has not been determined yet, and discontinuation of treatment is not recommended due to the potential for relapse [29].

Age-related changes in renal structure and function have been described, and an association between age and decreasing GFR has been suggested by several studies [30, 31]. Although the present study did not include a control group, the mean decrease in estimated GFR was significantly different from a sample of healthy volunteers and also different from volunteers taking antihypertensives and/or diuretics from a longitudinal study by Lindeman et al. [28], what makes it unlikely that the observed decrease in estimated GFR is exclusively due to aging. The mean decrease of ~3 ml/min/1.73 m$^2$/year observed in the present study is clinically relevant, as patients will be...
exposed to imatinib therapy for an extended period of time, probably for lifelong. Consequently, the estimated GFR may become lower than the lower limit of normality in a substantial proportion of patients. In this study, 12% of patients who had a baseline estimated GFR >60 ml/min/1.73 m² developed chronic renal failure during a median follow-up of 4.5 years.

The incidence of acute kidney injury observed in this study is higher than observed in clinical trials. Contrary to what would be expected, patients who developed acute kidney injury were young (age range 22–50 years) and had preserved renal function at baseline (estimated GFR range 88–147 ml/min/1.73 m²). Uric acid and potassium concentrations remained below the levels considered diagnostic for tumor lysis syndrome, what suggests that other mechanisms are implicated. As all these patients had previously been treated with IFN-α, a possible explanation for the observed renal function decline is a cumulative nephrotoxic effect of IFN. IFN-α has been observed to directly affect proximal tubular integrity by inducing apoptosis in tubular epithelial cells and impairing epithelial barrier function [32]. So, patients who have previously been exposed to IFN may have a higher propensity to develop acute kidney injury when subsequently exposed to imatinib, which may affect the same tubular cells [13]. Other authors have also suggested that a prior renal insult might predispose to imatinib-induced renal failure. In a phase II trial of patients with renal cancer, nephrotoxicity was more common in patients who underwent nephrectomy [33].

An important advantage of the present study is that there was no exclusion related to age, baseline serum creatinine, or risk factors for nephrotoxicity. The significant decrease in estimated GFR associated with the duration of imatinib therapy was independent of other factors, such as age, hypertension, diabetes, underlying chronic renal failure, and previous IFN treatment.

These findings suggest that the renal function of patients under imatinib therapy should be periodically monitored. Renal dysfunction is a common side-effect of chemotherapeutic agents, and it was also observed with other tyrosine kinase inhibitors [12, 13, 34]. It is often unrecognized by the treating physicians, who usually base their diagnosis on serum creatinine levels. However, several studies showed that serum creatinine level is not a sensitive estimator of renal function. Patients with a GFR as low as 60–80 ml/min/1.73 m² may still have serum creatinine <1.0 mg/dl due to an increase in the proximal tubular creatinine secretion. This may give the physician the wrong impression that the renal function is still normal [22, 35]. Therefore, the use of formulas to estimate the GFR or other methods that measure GFR is crucial and should be carried out routinely.

Table 6. Mean decrease in the estimated glomerular filtration rate per year according to baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>eGFR decrease (ml/min/1.73 m²/year)</th>
<th>Standard error (ml/min/1.73 m²/year)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>2.9</td>
<td>4.2</td>
<td>0.543</td>
</tr>
<tr>
<td>&gt;45</td>
<td>2.5</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.6</td>
<td>3.4</td>
<td>0.671</td>
</tr>
<tr>
<td>Female</td>
<td>2.9</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.5</td>
<td>2.6</td>
<td>0.618</td>
</tr>
<tr>
<td>Normotensive</td>
<td>2.8</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.8</td>
<td>2.8</td>
<td>0.924</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2.7</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Previous IFN treatment</td>
<td>2.6</td>
<td>3.2</td>
<td>0.338</td>
</tr>
<tr>
<td>No IFN treatment</td>
<td>3.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>CRF at baseline</td>
<td>2.1</td>
<td>2.1</td>
<td>0.543</td>
</tr>
<tr>
<td>Normal renal function at baseline</td>
<td>2.8</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; IFN, interferon-α; CRF, chronic renal failure.

Figure 1. Individual plots of serial estimated glomerular filtration rate (GFR) over time for representative subjects without chronic renal failure at baseline.
Limited data are available regarding the preventive strategies to avoid drug-induced nephrotoxicity. It is advisable to avoid concomitant administration of potential nephrotoxic agents (e.g. radiocontrast agents, aminoglycosides, nonsteroidal anti-inflammatory drugs) whenever possible because they may potentiate the renal toxicity and lead to a cumulative impairment in renal function [36]. Vomiting and diarrhea, which have been reported as side-effects of imatinib therapy in 16.9% and 32.8% of patients [15], respectively, should be monitored closely, and most often prevented to avoid dehydration. Loop diuretics, which are frequently used to relieve peripheral edema, should be prescribed with caution.

Further studies are necessary to elucidate the exact mechanisms of imatinib-induced nephrotoxicity. This might enable the development of reengineering strategies to produce compounds with reduced toxicity while retaining anticancer activity [37].

The present study has some limitations. The study sample consisted of a selected cohort of CML patients, as the enrollment was carried out in a single center. It is part of an observational study that was initially designed to evaluate imatinib-induced cardiotoxicity. Therefore, patients with cardiac disease, who have shown to be at increased risk for drug-induced nephrotoxicity [36], were excluded. The data were collected from the medical records, and the number of measurements differed among patients. Furthermore, only CML patients were enrolled. The effectiveness of imatinib has been demonstrated in several other diseases [3, 38, 39, 40] and it is also important to evaluate nephrotoxicity in these patients, as it is not known whether the propensity to develop imatinib-induced nephrotoxicity is related to the underlying malignancy.

conclusions

In conclusion, physicians should be aware that imatinib treatment may result in acute kidney injury and that the long-term treatment may cause a significant decrease in the estimated GFR and chronic renal failure. Therefore, it is important to monitor renal function of CML patients under imatinib therapy by measuring the creatinine levels and estimating GFR. Attention must be paid to concomitant administration of other potentially nephrotoxic agents, to avoid additive nephrotoxicity in these patients.

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disclosure

The authors declare no conflict of interest.

references


