Crizotinib Effects on Creatinine and Non-Creatinine–Based Measures of Glomerular Filtration Rate

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Introduction: Rapid reductions in creatinine-based estimates of the glomerular filtration rate (GFR) have recently been reported secondary to crizotinib use. Whether these reflect drug-induced changes in the true GFR or the validity of creatinine as a measure of kidney function in the presence of crizotinib is unknown.

Methods: Two anaplastic lymphoma kinase–rearranged non–small-cell lung cancer patients (one with pre-existing renal impairment) were identified during periods of time on and off crizotinib. Creatinine- and iothalamate-based estimates of renal function were conducted in the presence and absence of crizotinib.

Results: Crizotinib is associated with both acute and chronic effects on kidney function. Chronic creatinine changes seem to reflect a true reduction in the GFR. In contrast, acute effects include a reduction in creatinine-based estimates of the GFR without a reduction in non-creatinine–based measurements (consistent with, e.g., an acute effect of crizotinib on creatinine secretion), in addition to some reduction in the true GFR (with this latter effect seeming to be more prominent in the presence of pre-existing renal impairment).

Conclusion: If crizotinib-associated changes in creatinine-based kidney function suggest a change in dosing with either crizotinib or concomitant medications that are renally excreted, use of a non-creatinine–based assessment of kidney function, such as iothalamate assessments, should be considered before making a final decision.

Key Words: Anaplastic lymphoma kinase, Crizotinib, Creatinine, Glomerular filtration rate.

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Crizotinib is a small-molecule, ATP-competitive, inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and mesenchymal-epithelial transition (MET).[1–3] Known side effects include gastrointestinal disturbance, elevated transaminases, rapid reduction in free testosterone levels in the majority of men taking the drug, and asymptomatic bradycardia.[4–6] We recently reported apparent effects on kidney function as another side effect of crizotinib.[7] Specifically, crizotinib rapidly produces a mean 23.9% drop in the creatinine-derived estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation that could not be accounted for by dehydration, by tumor lysis, or by the use of concomitant known nephrotoxic drugs or intravenous contrast.[7–9] The majority of changes in eGFR occurs within 2 weeks of starting the drug and then plateaus. On cessation of dosing, eGFR was recoverable to 84% of baseline values or above in all patients. Based on these data, we rejected the idea that crizotinib was directly nephrotoxic. Instead, within our initial report, we raised two possible mechanistic hypotheses: either crizotinib was somehow interfering with a proportion of kidney function or it was altering the validity of creatinine as a measure of kidney function. This latter mechanism could occur, for example, through crizotinib competing with creatinine for secretion into the urine within the renal tubules, as has been described for some other drugs.[10,11] Here, we present matched creatinine-based estimates of eGFR and direct measurements of the GFR using urinary creatinine clearance and/or iothalamate assessments in two patients both on and off crizotinib to inform this debate.[12]

PATIENTS AND METHODS

Two ALK-rearranged non–small-cell lung cancer patients (one with pre-existing renal impairment) were prospectively identified during periods of time on and off crizotinib. Vital signs and creatinine- and iothalamate-based estimates of renal function were conducted in the presence and absence of crizotinib. The data were retrieved from patient electronic medical records in accordance with University of Colorado Institutional Review Board–approved protocol 09-018.

RESULTS

Case 1

A 53-year-old white male patient with stage IV adenocarcinoma of the lung developed chronic renal impairment secondary to initial chemotherapy exposure (six cycles of carboplatin and paclitaxel, followed by five cycles of cisplatin and pemetrexed and 12 cycles of maintenance pemetrexed). He initially had a complete response to the chemotherapy, but

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18 months after the end of the chemotherapy his disease progressed. At this point, he had been identified as ALK positive and was started on crizotinib, at which point his pretreatment creatinine was 2.05 mg/dl. He had a good radiographic response but was deemed intolerant of the drug due to recurrent elevations in serum creatinine associated with its use at all doses from 250 mg twice daily to 200 mg on alternate days, and crizotinib was discontinued.[7] His disease remained largely in remission off crizotinib, with isolated areas of growth being controlled with stereotactic body radiation therapy. When further tumor growth manifested in his liver, due to our increased awareness of the potential reversibility and limited cumulative effect of crizotinib on renal function, it was considered safe to rechallenge with crizotinib 250 mg twice daily, in conjunction with increased vigilance of his renal function. Three days before recommencing crizotinib, his blood pressure and heart rate were 123/75 and 57 beats per minute (bpm), respectively. His serum creatinine was 2.09 mg/dl, his eGFR calculated using the CKD-EPI prediction equation was 34 ml/min per 1.73 m^2, and his creatinine clearance measured through a 24-hour urine collection was 47.38 ml/min per 1.73 m^2 (1426 mg creatinine/day in urine). After being on crizotinib for 15 days, his serum creatinine was 2.64 mg/dl, his eGFR calculated using the CKD-EPI equation was 26 ml/min per 1.73 m^2, and his creatinine clearance measured through a 24-hour urine collection was 34.90 ml/min per 1.73 m^2 (1307 mg creatinine/day in urine). Urine microscopy was unremarkable and did not show any evidence of acute tubular necrosis (i.e., granular casts or renal tubular epithelial cells). Vital signs were available 30 days after being on crizotinib and showed a blood pressure and heart rate of 118/68 and 43 bpm, respectively. He had a complete metabolic and radiographic response on his first positron emission tomography/computed tomography scan performed after 6 weeks of therapy.

After approximately 5 months of therapy, his creatinine was recorded as 3.22 mg/dl, with a CKD-EPI eGFR of 20 ml/min per 1.73 m^2, and the decision was made to discontinue his crizotinib. His scans still showed no evidence of active disease, although his carcinoembryonic antigen (CEA) had increased from 18.6 at baseline to 49.9 ng/ml. His blood pressure and heart rate at this point were 115/68 and 46 bpm, respectively. On the last day of dosing with crizotinib, there had been some spontaneous improvement in his apparent renal function compared with the recordings 6 days beforehand. Specifically, his creatinine was 2.61 mg/dl, with a CKD-EPI eGFR of 26 ml/min per 1.73 m^2. An iothalamate assessment obtained on the same day showed a GFR of 37.3 ml/min per 1.73 m^2. He discontinued his crizotinib, and 23 days later his creatinine had fallen to 2.14 mg/dl, his CKD-EPI eGFR had increased to 33 ml/min per 1.73 m^2, his CEA had fallen to 24.9 ng/ml, and a repeat iothalamate assessment showed his GFR to have increased to 70.7 ml/min per 1.73 m^2 (Figs. 1 and 2*A*). Thirty days after crizotinib, his blood pressure and heart rate were 108/65 and 64 bpm, respectively. The patient was not on any known nephrotoxic medication, and, apart from the cessation of his crizotinib, there were no other changes in medication use during this time.

Case 2

A 70-year-old white male with stage IV adenocarcinoma of the lung was initially treated with carboplatin, pemetrexed, and zoledronic acid for four cycles. Subsequent molecular testing confirmed him to be ALK positive by fluorescence in situ hybridization analysis, and he commenced crizotinib at 250 mg twice daily. After 25 months of therapy, he developed oligoprogression in his sacrum and proximal left humerus and was treated with stereotactic body irradiation.[13] After 4 months, he developed decreased vision in his right eye and was found to have a new retinal lesion and referred again for radiation therapy. A magnetic resonance imaging of his brain was unremarkable at the time.

At the start of his initial crizotinib therapy, his blood pressure and heart rate were 168/70 and 87 bpm, respectively,

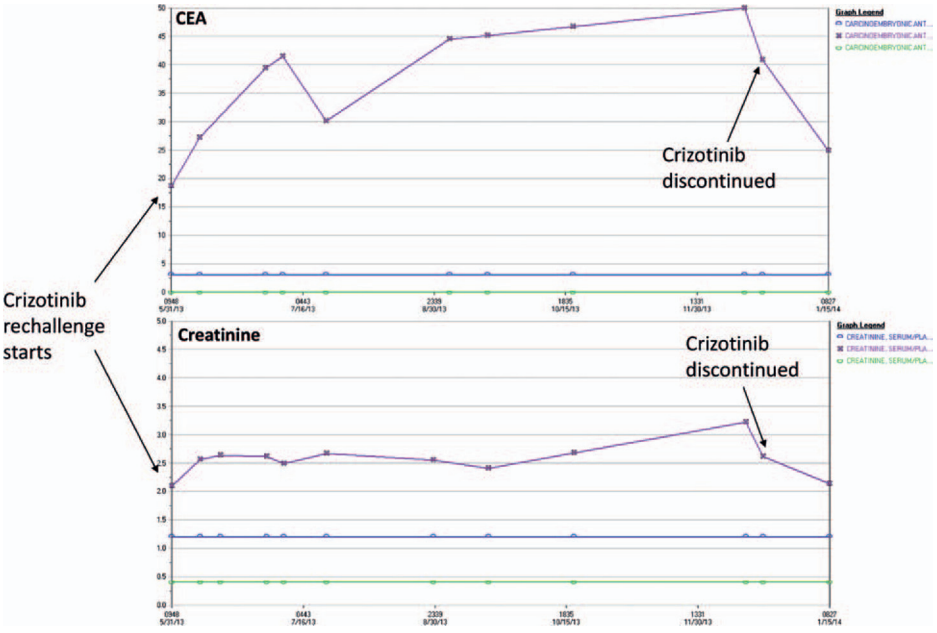

FIGURE 1. Changes in serum creatinine and carcinoembryonic antigen (CEA) levels on commencement and cessation of crizotinib treatment in a patient with pre-existing renal impairment. Units of CEA (ng/ml) and creatinine (mg/dl) are shown on the *y* axis and dates of measurements on the *x* axis. The green and blue horizontal lines represent the lower and upper limits of normal of each assay, respectively. Of note, CEA is known to be renally excreted, and the patient had a complete metabolic and radiographic response on positron emission tomography/computed tomography scanning that occurred rapidly and persisted during this period of time, despite the changes in CEA.

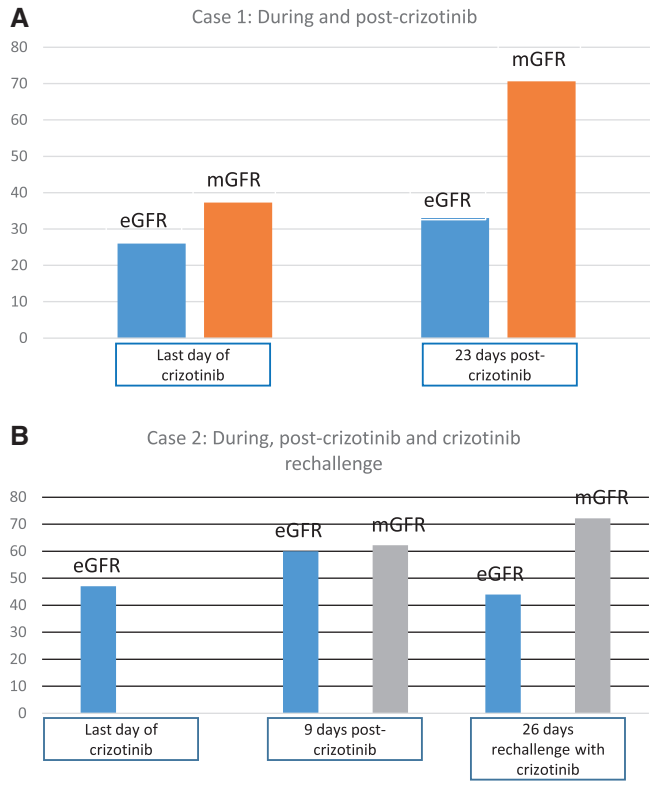

FIGURE 2. Changes in creatinine-based estimates of the glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (estimated GFR [eGFR]) and in non-creatinine–based measurements of the GFR using iothalamate assessments (measured GFR [mGFR]). *A*, In the patient with pre-existing renal impairment shown in Figure 1, assessments were made while on crizotinib and then after holding crizotinib for 23 days, showing a minor improvement in the eGFR and a large improvement in the mGFR, consistent with some direct effect of crizotinib on true renal function, as supported by the changes in CEA independent of changes in radiographic tumor activity (see text). *B*, In a patient holding crizotinib for 9 days and then restarting the drug, although there was a reduction in the eGFR on restarting, the mGFR actually increased, suggesting that some acute effect of crizotinib on creatinine secretion could also be occurring.

his serum creatinine was 0.84 mg/dl, and his eGFR was 89 ml/min per 1.73 m^2 using the CKD-EPI equation. After nearly 2.5 years on crizotinib, before holding his drug for retinal radiation therapy, his serum creatinine had increased to 1.45 mg/dl and his eGFR decreased to 47 ml/min per 1.73 m^2 using the CKD-EPI equation. His blood pressure and heart rate on his last day of dosing were 149/66 and 67 bpm, respectively. After being off drug for 9 days, his serum creatinine had fallen to 1.2 mg/dl and his eGFR had increased to 60 ml/min per 1.73 m^2 using the CKD-EPI equation. An iothalamate assessment performed within 24 hours of these blood results showed a direct measurement of his GFR to be 62.2 ml/min per 1.73 m^2. Blood pressure and heart rate were not recorded while off the crizotinib. After 11 days, he then restarted on crizotinib at 250 mg twice daily, and all measurements were repeated after 26 days. At this point, his serum creatinine had increased to 1.53 mg/dl and his CKD-EPI eGFR fallen to 44 ml/min per 1.73 m^2 using the CKD-EPI equation. However, a second iothalamate assessment performed within 24 hours of these blood results while back on crizotinib showed his GFR to be higher than when off the crizotinib at 72.2 ml/min per 1.73 m^2 (Figs. 1 and 2*B*). The patient did not have elevated CEA before, during, or after crizotinib exposure. Apart from the cessation and reintroduction of his crizotinib, there were no changes in any of his other medications during this time.

DISCUSSION

Our initial observation of the effect of crizotinib on serum creatinine and eGFR, the rapid onset and then plateauing of the effect, and equally rapid reversibility raised several etiological questions,[7] specifically, whether these data reflected a true effect of crizotinib on kidney function or only on the accuracy of this particular method for assessing it, for example, through an effect on creatinine secretion. From case I, who had pre-existing renal damage, it is clear that crizotinib can affect both urinary creatinine clearance and iothalamate-based direct measures of the GFR, in addition to the creatinine-based eGFR. After 15 days of dosing, there was a 26% rise in creatinine, a 24% drop in eGFR as assessed by the CKD-EPI equation, and a 26% drop in the measured GFR as assessed by urinary creatinine clearance. Subsequently, on cessation of dosing with crizotinib, the patient manifested an 18% drop in serum creatinine (bringing the creatinine close to his pre-crizotinib levels), a 27% increase in eGFR as assessed by the CKD-EPI equation, and an 89% increase in GFR as assessed by iothalamate (Figs. 1 and 2*A*). Iothalamate-based estimates of the GFR assume a "normal" distribution of intracellular and extracellular fluid. Beyond the background variability of the assessment (which has a reported coefficient of variation on repeated measurements of approximately 6–12%), only a true change in the GFR or significant changes in extravascular fluid accumulation (which did not occur) could explain the changes in the iothalamate readouts.[12] In addition, CEA, a serum tumor marker that is known to be renally excreted, which had been rising coincidently with the rise in creatinine, despite a rapid and persistent metabolic and radiographic complete response, then manifested a 50% reduction after cessation of dosing with crizotinib, despite no other change in the patient's anticancer therapy or additional radiographic change in his cancer (Fig. 1).[14] Given the changes in both iothalamate readings and CEA, a true effect of crizotinib on GFR has to be concluded, although an additional creatinine secretion effect cannot be ruled out. Certainly, the decrease in urinary creatinine (8%) with crizotinib in this one patient was below the mean reduction seen with other drugs that are known to interfere with creatinine secretion but was still within the range reported.[15] An acute event may have been associated with the immediate rise in the creatinine at the point when the decision was made to discontinue the patient's dosing as these values were improving before discontinuing dosing. However, the overall trend had been of worsening renal function for several months previously, and as values fell further on discontinuation of crizotinib dosing, consistent with our prior recovery data set,

the contribution of crizotinib exposure to the measured GFR readings remains unequivocal.[7] How much the effect on the measured GFR reflects a direct effect of crizotinib on the kidney, for example, through pharmacological inhibition of, as yet unknown, kinases involved in kidney function, versus an indirect effect, for example, secondary to renal hypoperfusion due to crizotinib-associated bradycardia remains uncertain. His blood pressure at the time of the bradycardia was neither markedly reduced nor elevated (115/68), but this does not preclude an effect of the bradycardia on cardiac output and consequently on renal perfusion per se as the local vasculature in the kidneys may not be reflective of the whole.

Case 2 also demonstrated results potentially consistent with both slow-onset direct effects of crizotinib on the GFR and rapid-onset effects on creatinine secretion. Of note, unlike case 1, case 2 did not have pre-existing kidney damage, and although there was again a suggestion of a crizotinib-associated reduction in heart rate from baseline values, his heart rate never reached the bradycardic levels of case 1. Prolonged exposure to crizotinib was associated with a 73% increase in the patient's creatinine and a 47% reduction in his eGFR, as assessed by the CKD-EPI equation, values too high to be explained by a pure creatinine secretion effect.[10,11] Subsequently, exploiting a break in crizotinib dosing for radiation therapy to obtain measures of kidney function taken before and after crizotinib exposure, cessation of crizotinib dosing was associated with a rapid 17% drop in serum creatinine and a 28% increase in eGFR as assessed by the CKD-EPI equation. Importantly, on recommencement of crizotinib dosing, although, as expected, there was a 28% rise in serum creatinine and a 27% decrease in eGFR as assessed by the CKD-EPI equation, there was no decrease in the measured GFR by iothalamate; instead there was actually a 16% increase in GFR from the initial iothalamate assessment. Assuming that some degree of intrapatient variability in iothalamate readings may be allowed for or that ongoing treatment of the underlying cancer may be marginally beneficial to renal function, here the suggestion is that crizotinib is not acutely affecting the true GFR but only the creatinine-based estimates of GFR, consistent with, for example, an effect on creatinine secretion.

Overall, these two cases illustrate what may be a range of different effects on kidney function associated with crizotinib use. Whereas in some situations crizotinib's effects on kidney function may be restricted to interfering with assessments that are creatinine-based with minimal to no effect on the "true" GFR, in other situations, particularly after prolonged exposure, a clear reduction in the "true" GFR assessed through multiple different means can occur. Consequently, consistent with our previous recommendations, if crizotinib-associated changes in creatinine-based kidney function are making practitioners consider a change in dosing with either crizotinib or concomitant medications that are renally excreted, use of a non-creatinine–based assessment of kidney function, such as iothalamate assessments, should be considered before making a final decision.

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