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Acute Tubular Injury and Renal Arterial Myocyte Vacuolization Following Crizotinib Administration



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INTRODUCTION

Considerable part (19.4%) of the total cancer deaths (1.59 million deaths worldwide) in 2012 were related to lung cancer.¹ It is estimated that more than 200,000 new cases of lung cancer will develop and up to 158,000 resulting deaths will ensue.² Out of this large number, non-small cell Lung cancer (NSCLC) presents itself as the most common lung cancer (90%) and is associated with significant morbidity and mortality. Amid the genetic characteristics of NSCLC, echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) mutation, which translates into a fusion-type protein tyrosine kinase, offers a promising therapeutic interest. This mutation occurs in a distinct subgroup of NSCLC patients (3%–5%) and generally presents in patients who have histology characteristic of adenocarcinoma, are younger, and have little or no smoking history. Crizotinib is the first synthesized member of the ALK inhibitor family targeting this ALK mutation. It was approved by the US Food and Drug Administration for ALK inhibition in NSCLC. Phase III trials (PROFILE 1007, PROFILE 1014) confirmed the superior efficacy of crizotinib in the treatment of ALK-positive NSCLC.³

As with other recently released targeted agents, renal adverse renal effects have been observed (Table 1), including acute kidney injury (AKI) (Camidge DR, Bang Y, Kwak EL, et al. Progression-free survival (PFS) from a phase 1 study of crizotinib (PF-02341066) in patients with ALK positive non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol*. 2011;29(Suppl):abstract 2501).⁴

We came across a special case of worsening chronic kidney disease under crizotinib treatment with 2

characteristics: AKI and acute tubular injury occurred late, almost 1 year after crizotinib initiation, and histologically, by the presence of unusual arteriolar myocyte vacuolization.

PATIENT PRESENTATION

A 71-year-old woman with EML4-ALK gene translocation metastatic NSCLC (T4N0M1b; pleural, lymph nodes, chest wall, lung) was treated with crizotinib as third-line therapy starting December 2015. First chemotherapy lines included cisplatin (2013) and paclitaxel + carboplatin AUC 5 (2014) after superior right lobectomy (2005).

Her past medical history was unremarkable besides stage IIIB vascular chronic kidney disease (CKD).

Crizotinib was administered orally 250 mg twice daily and started after discontinuation of the previous drugs. Renal function was characterized by a serum creatinine level of 100 μmol/l and the estimated glomerular filtration rate (eGFR) as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was 46 ml/min per 1.73 m² corresponding to stage IIIB of the KDIGO classification.

She was referred to the Nephrology department for worsening of renal function showing at that moment serum creatinine (sCr) values of 130 μmol/l and CKD-EPI 35 ml/min per 1.73 m². At that time, UPCr was 0.1 g/g with unchanged urinary sediment. Her daily medication at that time included bisoprolol 2.5 mg, rilmenidine 2 mg, omeprazole 40 mg, and ezetimibe 10 mg. No evidence of obstructive urinary disease and no renal cyst were observed on abdominal computed tomographic scan.

Table 1. Teaching points

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|--|
| Crizotinib is an ALK inhibitor drug, FDA approved in NSCLC |
| Crizotinib induced a rise in serum creatinine during the first 12 wk of therapy. Cessation of treatment was associated with a relatively rapid recovery, generally within the first week of drug discontinuation |
| No clear physiopathologic explanation for crizotinib influence on renal function |
| Nephrotoxic effects of crizotinib included |
| - Edema formation |
| - Electrolyte abnormalities: water, sodium, and phosphate disturbances |
| - Acute and chronic kidney disease, related to |
| * Pseudo-AKI: interference in serum creatinine dosage, competitive inhibition of creatinine tubular secretion |
| * True kidney injury: acute tubular injury |
| * Renal arteriolar myocyte vacuolization |
| - Renal cyst formation and progression |
| Kidney biopsy study is needed for understanding of the renal damage in crizotinib-treated patients. |

ALK, anaplastic lymphoma kinase; FDA, US Food and Drug Administration; NSCLC, non-small cell Lung cancer.

Given the possibility of false degradation of renal function in relation to either pharmacologic interference in serum creatinine dosage or a competitive inhibition of creatinine tubular secretion within crizotinib treatment, renal function was evaluated using cystatin C (CysC). sCysC and Cys-estimated GFR was abnormal [sCysC 1.41 mg/l (N 0.62–1.11), CysC GFR 61 ml/min (N 80–170)] even if they remain higher than estimated from sCr by CKD-EPI.

Progressive and unexplained renal function worsening (sCr 140 then 160 $\mu\text{mol/l}$) prompted a kidney biopsy, performed by transjugular way on the 11th month after the start of crizotinib.

A total of 25 glomeruli were sampled, of which 14 were normal and 11 were obsolete. The biopsy demonstrated 2 types of lesion including acute tubular injury without interstitial cell infiltration (Figure 1) and renal arteriolar myocyte vacuolization (Figure 2). Immunofluorescence examination for IgA, IgM, IgG, C3, C1q, kappa, lambda, albumin, and fibrinogen was negative. Electron microscopy was not performed.

Based on the Naranjo Probability Scale, the likelihood of crizotinib-induced renal injury in this case was probable (score 7).

DISCUSSION

Only a few dozens of cases of nephrotoxicity related to crizotinib use in NSCLC were reported.

In the earliest, albeit largest, series of 38 patients, a rise in serum creatinine or reduced eGFR was noted during the first 12 weeks of therapy, mostly the first 2 weeks.⁵ The mean and median baseline eGFRs were 82.6 ml/min per 1.73 m² and 78.4 ml/min per 1.73 m², respectively. Of these patients, 4 had underlying CKD. Interestingly, there was a mean 23.9% decrease in eGFR over the first 12 weeks. Cessation of crizotinib

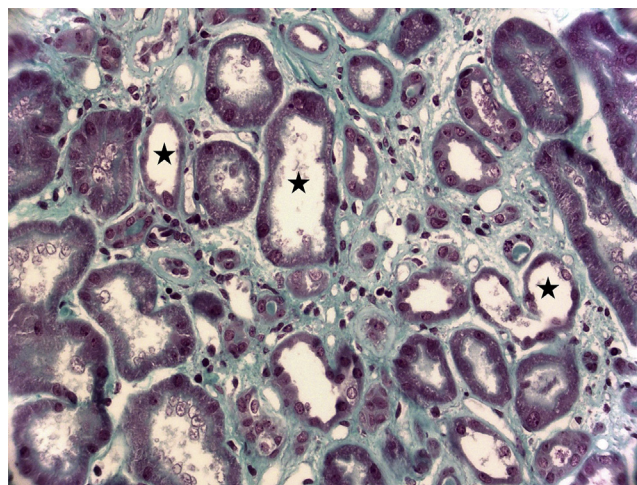


Figure 1. Acute tubular injury with regenerative changes including flattening of epithelial cells, cytoplasmic basophilia, and heterogeneity in cell size (star) (Masson trichrome. original magnification $\times 400$).

was associated with a relatively rapid recovery of eGFR (average of 35.5%), generally within the first week of drug discontinuation. Overall, eGFR recovery was complete in 56.3% of cases, whereas the remaining patients had partial renal recovery to 84% to 97% of baseline. No renal histologic data were available.

Three case reports describe AKI related to crizotinib administration in a setting of NSCLC.

Gastaud *et al.*⁶ reported an AKI in a 49-year-old patient with previous totally normal kidney function. Within 3 weeks of crizotinib therapy, serum creatinine increased from 0.8 to 2.6 mg/dl. Crizotinib discontinuation was associated with kidney function improvement (serum creatinine improved to 1.6 mg/dl) within 8 days. Drug rechallenge was associated with a rapid decline in kidney function (serum creatinine increase to 3.8 mg/dl). Kidney biopsy revealed diffuse acute tubular injury/acute tubular necrosis.

Martorell *et al.* reported another case of crizotinib-associated AKI in a patient with stage 3b CKD before Crizotinib challenge.⁷ Serum creatinine was stable at 2.7 mg/dl. Two weeks after crizotinib therapy, serum creatinine rose from 2.7 to 3.0 mg/dl and the dose was reduced by half. Kidney function continued to worsen (serum creatinine 3.46 mg/dl) at 3 weeks, the drug was discontinued, and serum creatinine declined back to 2.73 mg/dl. A reduced dose of crizotinib was reintroduced 2 months later, but kidney function deteriorated after 2 weeks and returned to pretreatment values 1 month after definitive cessation.

Fukuizumi *et al.* describe an 81-year-old man with a postoperative grade 2 (CTCAE version 4.0) AKI case in a setting of grade 3 congestive heart failure, after only 5 days of crizotinib at the usual 250-mg twice-daily dose.

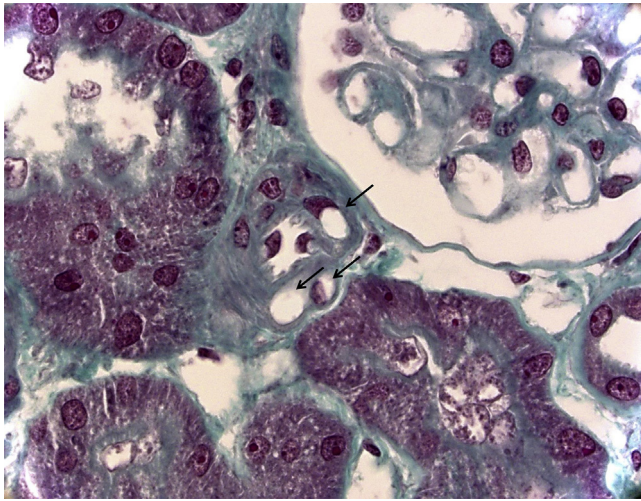


Figure 2. Vacuolization of the arteriolar myocytes (arrows) (Masson trichrome, original magnification $\times 1000$).

Crizotinib was then administered at a dose of 250 mg twice daily only every 3 days for 13 months with maintenance of the antitumor effect, but no information was available on renal function.⁸

There is no clear physiopathologic explanation for crizotinib influence on renal function. We believe mesenchymal epithelial transition growth factor (c-Met) expression in the normal adult nephron could partially explain this toxicity. MET is known to be expressed at the proximal convoluted tubules, as well as the proximal loop of Henle and the distal convoluted tubule. Inhibition of the c-Met pathway may underlie peripheral edema, one of the described nephrotoxic late-onset, cumulative effects of crizotinib. Creatinine secretion inhibition at the proximal convoluted tubule through a competitive mechanism could also give a partial explanation.

Kidney biopsy study is needed for further understanding of the renal damage in crizotinib treated patients. In addition to mostly tubular lesions (acute interstitial/acute tubular necrosis) in the available

records, Gastaud and colleagues⁶ case showed some arteriolar lesions, including minimal/focal glomerular mesangiolytic, whereas in our case, characteristic arteriolar myocyte vacuolization mimicking calcineurin inhibitors-induced arteriopathy was noted, supporting a causative role for crizotinib in this phenomenon.

Practitioners in the onco-nephrology field, should be aware of the possible adverse renal effects of crizotinib to allow adequate management.

DISCLOSURE

All the authors declared no competing interests.

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