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Case report

Crizotinib and renal insufficiency: A case report and review of the literature

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ABSTRACT

A 69 year old man with idiopathic chronic kidney disease was diagnosed with relapsing EGFR negative, ALK positive lung adenocarcinoma, and treated with chemotherapy and antiangiogenic treatment, under which his renal insufficiency worsened. During second line crizotinib treatment, further worsening of the renal function was seen, with very clear correlation with crizotinib withdrawal and rechallenge. No further drug causes for the worsening blood creatinine values were detected.

1. Introduction

Crizotinib treatment has become a very important treatment for ALK translocated metastatic adenocarcinoma of the lung, showing much higher responses and longer time to disease progression as compared to conventional chemotherapy regimens [1–3]. However, due to its accelerated approval in 2011 based mainly on phase I data, we are still in the process of acquiring knowledge on its toxicity profile and consequences on the long run. As with many other targeted therapies, this will be achieved through prolonged treatment of a higher number of patients.

We report on a case of worsening chronic kidney disease under crizotininb treatment, and review the data on the subject.

2. Case

A 69 year old man, 59 kg and 160 cm, presented in 2006 with a fetal type adenocarcinoma of the lung. As medically relevant history he referred an ischemic ictus two months before the oncologic diagnosis, mild blood hypertension without pharmacologic treatment at that point, diabetes mellitus type 2, benign prostate hyperplasia and a past smoking history of 35 pack years. He underwent a superior right lobectomy which confirmed a radiologically staged fetal type adenocarcinoma of the lung pT1 pN0 M0. No adjuvant chemotherapy or radiotherapy was deemed necessary for his stage IA disease, and he underwent regular follow up.

In February 2008 worsening renal function was detected. In 2010 he was referred to the Nephrology department for his chronic kidney disease (CKD), showing at that moment serum creatinine values of 1.85 mg/dl. The estimated glomerular filtration rate (eGFR) as determined by the Chronic Kidney Disease Collaboration Formula (CKD-EPI) was 37.1 ml/min/1.73 m^2, corresponding to stage 3b of the KDIGO classification. His medication at that time included ramipril, paracetamol/tramadol, escitalopram, pantoprazol, lorazepam, and alfusozine. His CKD was attributed mainly to this chronic hypertension and diabetes, so nephroangiosclerosis was the most probable underlying cause. No renal biopsy was carried out as the patient presented no relevant proteinuria and no abnormal urinary elements. No evidence of obstructive urinary disease was observed.

In November 2011, five years after the initial resection surgery, he referred an increase in his basal dyspnea. This motivated a thoracic and abdominal CT scan, which showed an endobronchial lesion and multiple bilateral milimetric lung nodules. A fiberbronchoscopy confirmed tumoral infiltration of the main right bronchus

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and carinal mucosa. Biopsies showed TTF-1 and CK-7 positive adenocarcinoma, confirming the local and systemic relapse. No EGFR mutations were found.

In January 2012 he was started on first line treatment for his relapsing lung adenocarcinoma with paclitaxel 175 mg/m^2, carboplatin AUC 5 and bevazicumab (antiangiogenic treatment) 7.5 mg/kg every 3 weeks. He received 6 cycles of combination treatment, showing partial tumoral response. All throughout this treatment he maintained stable creatinine values of 1.7 mg/dl. He then went on with bevacizumab 7.5 mg/kg maintenance treatment every 3 weeks, during which he developed worsening of his chronic kidney disease, with rising creatinine values up to a maximum of 2.73 mg/dl (CKD-EPI 23.2 ml/min/1.73 m^2, stage 4 of the KDIGO classification). In July 2012, after a minimal rise in the blood pressure values was detected, treatment with furosemide 20 mg/day was added, after which pressure values remained constant and controlled throughout the remaining antiangiogenic treatment. Urinary protein to creatinine ratio in October 2012 was 0.37 (normal range up to 0.20).

In March 2013 after a total of 21 cycles of bevacizumab, minimal progression of some the left lung nodules was detected. This, together with the worsening renal insufficiency prompted stopping the antiangiogenic treatment with bevacizumab.

An ALK translocation in more than 15% of the cells was detected at that point, and second line treatment with crizotinib 250 mg orally twice daily was started in April 2013, despite the scarce data available in renal insufficiency situations at that time, based on the mainly non-renal drug metabolism. The patient had at this point creatinine values of 2.70 mg/dl (CKD-EPI 23 ml/min/1.73 m^2).

Two weeks after the start of treatment, the patient had again rising serum creatinine values of 3.0 mg/dl (CKD-EPI 20.3 ml/min/1.73 m^2). No other drugs had been modified. A dose reduction to 200 mg twice a day was undertaken, despite which, the patient carried on with the worsening renal insufficiency with creatinine values of 3.46 mg/dl three weeks later (CKD-EPI 17.4 ml/min/1.73 m^2), corresponding to stage I of the AKIN classification. The rate of worsening CKD was thus significantly higher than previously presented by the patient on the basis of his comorbidities or during the angiogenic treatment. A rising lactate deshydrogenase (LDH) value was also observed. No haptoglobin determinations were carried out. Platelet count was rather stable throughout crizotinib treatment, as had been at baseline (Fig. 2). Crizotinib was then withdrawn for 2 weeks, during which the renal insufficiency improved to values of 2.73 mg/dl, with a clear decrease of the LDH values, thus returning to pre-crizotinib treatment values of CKD. The patient remained asymptomatic throughout, and no functional complications of the renal insufficiency seen (hyperkaliemia or metabolic acidosis). No renal biopsy was carried out as the risks of such a technique were deemed to outweight the benefits, taking into account the medical history of the patient. The tumoral evaluation in June 2013, two months after crizotinib treatment was initiated, showed radiologically stable and clinically asymptomatic disease.

Crizotinib reintroduction was attempted at a further reduced dose of 200 mg once daily, but after two weeks the creatinine values clearly rose again to values of 3.28 mg/dl. After this, crizotinib treatment was finally withheld (Figs. 1 and 2).

One month after definitive stopping of the treatment, the patient again showed improvement of the creatinine values (2.87 mg/dl).

It is important to note that, ever since the chronic kidney disease was detected, CT scans have been carried out without contrast most of the times, or under oral acetilcysteine protection if ever with intravenous iodine contrast. The patient has retained a very stable weight throughout his neoplasic history and treatment, and this is thus not expected to have caused significant changes in eGFR. Furthermore, no other drugs were introduced during crizotinib treatment which could account for the worsening renal function. Taking all this into account, the creatinine variations are scored as probably related to the drug on the Naranjo drug reaction probability scale (score 8) [4].

3. Discussion

The upcoming use of targeted therapies has confronted us with new and partially unknown secondary effects. It has been suggested that co-expression of shared targets between normal tissues and tumoral cells could underlie and explain some of these toxicities. Vascular endothelial growth factor (VEGF), for instance, the target of bevacizumab therapy, is strongly expressed in the embryologic developmental phase and plays a major role in vessel formation at that stage. It is further highly expressed in the fenestrated glomerulus epithelium. One of the most common secondary effects to angiogenic therapy is proteinuria secondary to damage to the glomerular filtration barrier, which appears in 20–65% of bevacizumab-treated patients. Nephrotic range proteinuria occurs in 1–2% of these. This renal toxicity has also been reported in relation to other antiangiogenic therapies such as sunitib or sorafenib. Other targeted therapies such as EGFR tyrosine kinase inhibitors (erlotinib or gefitinib) or anti-HER2 therapy (trastuzumab or lapatinib) have rarely been reported to result in renal injury [5–7].

Crizotinib treatment has become a very important treatment for ALK translocated metastatic adenocarcinoma of the lung, which comprises around 5% of all lung adenocarcinomas. This treatment shows much higher responses and longer time to disease progression compared to conventional chemotherapy regimens. However, due to its accelerated approval in 2011 based mainly on phase I data, little is still known on its toxicity profile and metabolic consequences [1–3].

Crizotinib is a multikinase inhibitor targeting the ALK, MET and ROS1 oncogenic tyrosine kinases at the tumoral cellular membrane. It is given at a standard dose of 250 mg taken orally twice daily. Common side effects thus far reported include visual disturbances, gastrointestinal disturbances such as nausea, diarrhea or constipation, peripheral edemas, interstitial lung disease and hypogonadism in males. Among laboratory abnormalities are elevated transaminases, hypophosphatemia and lymphopenia. Although it is mainly eliminated in the feces (63%), up to 22% of the elimination occurs in the urine. However, up to now little has been known about the safety of treatment in patients with underlying renal insufficiency, nor on its effects on renal function. The current formal recommendations are not to adjust dosage in patients with mild creatinine clearance [CRcl] (60–89 ml/min) or moderate (CRcl 30–59 ml/min), and to reduce dosage to 250 mg once a day in patients with severe renal insufficiency (CRcl < 30 ml/min) not requiring dialysis [8].

However, as more patients are treated worldwide with crizotinib, the toxicity profile regarding renal insufficiency becomes more clear. Gastaud et al. just recently reported on a male patient showing renal function deterioration during crizotinib treatment, who, just as our patient, showed creatinine improvement after stopping treatment, and which once again worsened after treatment re-challenge [9].

Further, Brosnan et al. have recently published a larger retrospective series of 38 stage IV crizotinib treated non-small-cell lung cancer patients, and analyzed the incidence of worsening renal function during treatment [10]. Their work has to be praised as it included both patients with normal baseline renal function, and underlying chronic kidney disease, as has helped much to clarify crizotinib's effect on kidney function. They recorded the