Journal on Oncology

www.journalononcology.org

Case Report

Open Access, Volume 2

Alectinib - Induced Acute Renal Failure: A Case Report

E Prado-Mel[1]; P Ciudad-Gutiérrez[1]*; A Sánchez-Martín[2]; L Abdel-Kader Martín[1]

[1]Hospital Pharmacy Department, Virgen del Rocío Hospital, Seville, Avda, Manuel Siurot s/n 41013, Spain.

[2]Hospital Pharmacy Department, Virgen de las Nieves Hospital, Granada, Avda, Fuerzas Armadas nº2, Spain.

Abstract

Background: Lung cancer is the most common cause of cancer death worldwide, and it is more frequent in men than women. It is estimated that lung cancer is responsible for approximately 1 in 5 cancer deaths. Alectinib is a potent and selective orally active tyrosine kinase inhibitor used for anaplastic lymphoma kinase-positive non-small cell lung cancer, which has a better safety profile than other inhibitors of anaplastic lymphoma kinase. We report the first case of a mixed pattern of acute interstitial nephritis and acute tubular necrosis provenby renal biopsy upon starting alectinib therapy.

Case presentation: A 68-year-old man with diabetes, hypertension and dyslipidaemia, diagnosed with anaplastic lymphoma kinase-positive non-small cell lung cancer stage IV, had 27 days previously started alectinib 600 mg twice daily. He presented at the emergency room due to vomiting, nausea and more dyspnoea than usual. A creatinine level 3 times higher than baseline, hyponatraemia and hypokalaemia were detected in laboratory tests. After a diagnosis of acute renal failure, the patient was admitted to hospital. Nephrotoxic drugs were suspended, and haemodialysis was required. After dismissing other causes, a possible diagnosis of acute interstitial nephritis due to alectinib intake was established. Corticotherapy was initiated; after 10 days of treatment, renal function began to return to baseline levels. Renal biopsy showed a mixed pattern of acute interstitial nephritis and acute tubular necrosis. The patient was discharged, and alectinib therapy was modified to lorlatinib. A cytochrome P540 3A pharmacogenetic test was performed, and no genetic polymorphisms were found. After 10 months with lorlatinib therapy, renal function remains stable and the patient maintains this therapy.

Conclusions: The relationship between acute renal failure and alectinib initiation is considered probable in this patient. Although it is a rare adverse effect reported in less than 1% of cases, it would be advisable to monitor renal function in patients starting this therapy, especially in those with renal failure.

Keywords: Alectinib; Acute tubular necrosis; Acute interstitial nephritis; Non-small cell lung cancer; Case report.

Abbreviations: ASA: Acetylsalicylic acid; AIN: Acute interstitial nephritis; ATN: Acute tubular necrosis; ALK: Anaplastic lymphoma kinase; ARF: Acute renal failure; CYP3A4: Cytochrome P540 3A; eGFR: Estimated glomerular filtration rate; NSCLC: Non-small cell lung cancer.

Manuscript Information: *Received: Jun 13, 2022; Accepted: Jul 08, 2022; Published: Jul 15, 2022*

Correspondance: *P Ciudad-Gutiérrez, Hospital Pharmacy Department, Virgen del Rocío Hospital, Seville. Avda, Manuel Siurot s/n 41013, Spain. Email: aghaeeat@mums.ac.ir*

Citation: *Prado-Mel E, Ciudad-Gutiérrez P, Sánchez-Martín A, Abdel-Kader Martín L. Alectinib - Induced Acute Renal Failure: A Case Report. J Oncology. 2022; 2(2): 1036.*

Background

Although lung cancer age-adjusted death rates have been falling 3.6% on average each year between 2009 and 2018 [1], it continues to be the leading cause of cancer death worldwide, with an estimated 1.6 million deaths annually. Approximately 85% of lung cancers are non-small cell lung cancer (NSCLC) [2]. Anaplastic lymphoma kinase (ALK) mutations are found in only 3% to 5% of NSCLC cases; however, they are also implicated in the pathogenesis of other neoplasms, such as rhabdomyosarcoma and neuroblastoma [3].

Alectinib is a targeted therapy used in patients with ALK-positive NSCLC as well as for those who have progressed or are intolerant to crizotinib. Alectinib has been found to be more effective than crizotinib in a first-line NSCLC setting [4]. The most common adverse reactions to alectinib are anaemia, dysgeusia, stomatitis and myalgias; whereas those of greater relevance in older people are diarrhoea, lack of appetite and serum bilirubin elevation [5,6].

Cytochrome P540 3A (CYP3A4) is an enzyme highly involved in the metabolism of alectinib and other ALK inhibitors, such aslorlatinib, whose genetic variants can contribute to interindividual variability of metabolic activity [7].

Alectinib-induced acute renal failure is a very rare adverse event that has been reported in less than 1% of the patients treated. The nephrotoxicity mechanisms have not thus far been elucidated; however, there is some evidence that it can cause renal impairment at the glomerular, interstitial or tubular level [8-10]. This clinical case describes a patients withALK-positive NSCLC treated with alectinib who required emergency dialysis due to an acute renal failure.

Case presentation

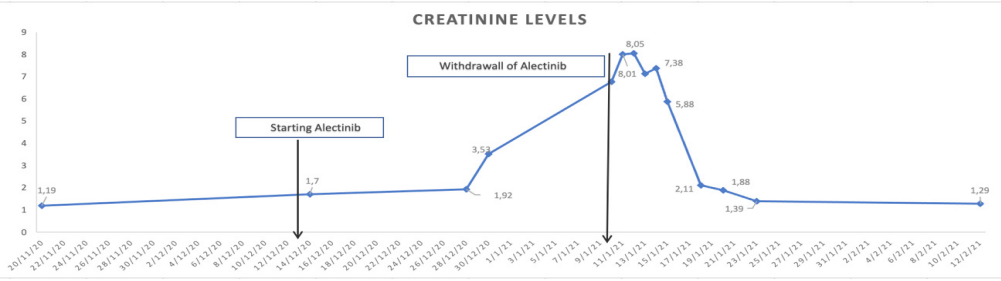
We describe a 68-year-old man with a recent diagnosis of ALK-positive primary metastatic NSCLC. The patient presented to the emergency room with moderate exertional dyspnoea without fever and 2 days of nausea and vomiting that did not subside with metoclopramide.

On examination, the patient appeared normally coloured andtachypneic with a good oxygen saturation (97%). He had rhythmic tones without murmurs. Respiratory auscultation of the left lung base revealed hypophonesis. The abdomen was soft and depressible and non-painful on palpation. There were no masses or megalies and no signs of peritonism. The patient had pretibial oedema in the lower limbs. A laboratory analysis showed that his serum creatinine was 6.46 mg/dl, urea 138 mg/dl, sodium 121 mEQ/L and potassium 5.8 mEQ/L. A chest X-ray revealed impingement of the right costophrenic sinus with an increase in left pleural effusion compared withprevious X-rays. Thus, the patient was diagnosed with acute renal failure (ARF) and was admitted to thenephrology department.

His medical history included a recent diagnosis, 2 months previously, of ALK-positive NSCLC with liver and bone metastases (T1bN2M1c, Stage IVc), dyslipidaemia, hypertension, insulin-dependent diabetes mellitus type 2, a previous myocardial infarction and a history of resected bladder tumour. He had been an exsmoker for 10 years, with no known allergies. His usual treatment included ramipril 10 mg/24 h, bisoprolol 2.5 mg/24 h, acetylsalicylic acid (ASA) 100 mg/24 h, atorvastatin/ezetimibe 20/10 mg/24 h, gliclazide 30 mg/12 h, metformin 850 mg/8 h, empagliflozin 10 mg/24 h, long-acting insulin every night and ranolazine 375 mg/12 h. He was started on alectinib 27 days previouslybecause of the diagnosis of ALK-positive metastatic NSCLC.

The first step was to stop the nephrotoxic drugs, such as ASA and oral antidiabetics. After analysing the chronological relationship between the start of alectinib and the development of ARF, alectinib was also discontinued. Renal failure was confirmed with a peak level of creatinine 8.05 mg/dl, urea 140 mg/dl and an estimated glomerular filtration rate (eGFR) <10 ml/min in a laboratory test 24h after admission. The renal biopsy showed sclerosis of 78% of the renal glomeruli, interstitial fibrosis of 33%, moderate and diffuse tubular necrosis and inflammatory infiltrate of the lymphoplasmacytic type. We suspected medication-related acute interstitial nephritis (AIN). Venovenous haemodialysis was required; 500 mg intravenous methylprednisolone was administered for 3 days, and subsequently 60 mg oral prednisolone.

After 10 days of systemic corticosteroids, the patient was discharged because of a rapid renal recovery with a significant decrease of creatinine (Table 1) and good diuresis. At discharge, short- and long-acting insulin were prescribed to control his diabetes. Oral titrated corticosteroids were also prescribed for a 2-month period. ASA had to be suspended for 20 more days. A pharmacogenetic test of CYP3A4 (alleles *1B, *1G, *22 and *3) and CYP3A5 (*3 and *6) was performed; however, no polymorphism was found in any of the alleles studied. Lorlatinib was started after discharge. After 10 months oftreatment with lorlatinib, the patient's renal status continues to be stable.



	20/11/20	14/12/20	28/12/20	30/12/20	10/1/21	11/1/21	12/1/21	13/1/21	14/1/21	15/1/21	18/1/21	20/1/21	23/1/21	12/2/21
Creatinine (mg/dl)	**1,19**	1,7	1,92	3,53	6,78	8,01	**8,05**	7,13	7,38	5,88	2,11	1,88	1,39	**1,29**

Table 1: Laboratory values during alectinib therapy.

	Baseline	4 weeks after starting alectinib	2 weeks upon stopping alectinib
Creatinine (mg/dl)	1.29 [0.7-1.5]	8.05 [0.7-1.5]	1.29 [0.7-1.5]
Urea (mg/dl)	69 [10-50]	140 [10-50]	83 [10-50]
Sodium (mEq/L)	135 [135-145]	129 [135-145]	135 [135-145]
Potassium (mEq/L)	4.2[3.5-5]	5.3 [3.5-5]	3.3 [3.5-5]
eGFR(ml/min)	57.36	9.19	57.36

eGFR: estimated glomerular filtration rate.

Discussion and conclusions

AIN is a type of kidney injury characterised by the presence of inflammatory infiltrates, oedema and tubulitis accompanied by acute renal failure [11]. The most common aetiology is the immunoallergic reaction associated with drug exposure, which typically appears within 7–10 days. The reversibility is characteristic of this reaction; thus, stopping the responsible agent is usually sufficient-to recover renal function to baseline levels [12,13]. In the present case, the patient showed a creatinine value of 3.53 mg/dl 10 days after starting treatment with alectinib. After the switch to lorlatinib, the patient's renal status continues to be stable, with no signs or symptoms of nephrotoxicity.

Recently, a few articles have been published highlighting the nephrotoxicity induced by ALK inhibitors. Specifically, Troxel et al, 2016 [14], have emphasised the relationship between some cancer therapies and tubulointerstitial disorder development. According to these authors, the use of crizotinib can trigger acute tubular necrosis (ATN) in some patients; however, there was no evidence that this drug could cause AIN. One case report by Ramachandran et al, 2018 [10], had documented that alectinib could trigger acute renal failure with reversible ATN in a patient without previous renal impairment. In our case, the results of the renal biopsy performed on the patient revealed renal injuries compatible with AIN and ATN, probably associated with alectinib treatment. Thus, other renal pathologies that could have been related to the episode of acute renal failure were ruled out.

It appears clear that ALK inhibitors can lead to an increase of serum creatinine, especially in the first 2 weeks of treatment. According to Brosnan et al, 2014 [15], 12 (26%) of 46 patients treated with crizotinib with a dose of 250 mg twice daily showed a marked decrease in eGFR in a period of 16 months. In most cases, however, this eGFR decrease reverted to baseline values after treatment suspension. The patient in our case experienced a rise in creatinine levels for more than 3 weeks after starting antineoplastic treatment. However, there are no specific recommendations for renal function monitoring in patients treated with alectinib, especially those with chronic renal failure.

In the AF-002JG trial, 47 patients with ALK-positive NSCLC who progressed or were intolerant to crizotinib received variable doses of alectinib, between 300 and 900 mg twice daily. All patients had adequate renal, haematological and hepatic function before starting the trial. Only 1 patient showed an episode of grade IV acute renal failure requiring haemodialysis while taking alectinib 460 mg twice daily. The patient had a family history of hyperoxaluria. After discontinuation of treatment for 1 month, alectinib was restarted at the same dose with a close monitoring of renal function [16]. The case of a patient with progressive renal failure 1 year after starting alectinib had also been reported, partially recovering his renal function with corticosteroid intake, with complete renal recovery after discontinuation of the drug [8].

To our knowledge, this was the first case of acute renal failure induced by alectinib evidenced through a renal biopsy with a possible mixed pattern of AIN and an ischaemic ATN, due to digestive losses and blockage of the renin angiotensin aldosterone system. The temporal relationship between the initiation of alectinib and the development of acute renal failure strengthen the idea that alectinib was the responsible drug for this event. In fact, after employing the causality assessment algorithm of Naranjo et al, 1981 [17], it was determined that the episode of acute renal failure was "probably" caused by alectinib. It is interesting to note that alectinib, which is excreted mostly by the hepatobiliary route (98%), can still cause nephrotoxicity. Some studies have suggested that alectinib-induced renal toxicity could be prevented by temporarily discontinuing the medication and restarting the treatment with a reduced dose. Other measures to reduce alectinib nephrotoxicity would be to avoid volume depletion in addition to avoiding the concomitant use of other nephrotoxic drugs [9].

Given that clinical experience remains limited, it would be advisable to monitor renal function in more patients receiving alectinib in order to reduce comorbidities and mortality and to improve clinical outcomes.

Declarations

Ethics and consent to participate: Not applicable.

Consent for publication: The authors have receivedwritten informed consent for publication from the patient.

Availability of data and materials: Data sharing is not applicable to this case report,given thatno datasets were generated or analysed during the current study.

Competing interests: The authors declare that they have no competing interests.

Funding: The present case report has not received specific aid from agencies from the public sector, commercial sector or nonprofit entities.

Acknowledgements: Not applicable.

Author contributions statement: E.P, P.C and L.A wrote the main manuscript text. E.P prepared table 1. A.S did the pharmacogenetic test from the Hospital Pharmacy Department, Virgen de las Nieves. Granada, Spain. All authors reviewed the manuscript.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results program. Available in: https://seer.cancer.gov/statfacts/htm.l/lungb.html
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018; 553: 446-454.
3. Izzedine H, El-Fekih RK, Perazella MA. The renal effects of ALK inhibitors. Invest New Drugs. 2016; 34: 643-9.

4. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017; 377: 829-838.

5. Yang JC, Ou SI, De Petris L, Gadgeel S, Gandhi L, et al. Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies (NP28673 and NP28761) of Alectinib in ALK-positive Non-Small Cell Lung Cancer. J Thorac Oncol. 2017; 12: 1552-1560.

6. Alecensa (Alectinib) EMA label: https://cima.aemps.es/cima/pdfs/es/ft/1161169001/FT_1161169001.pdf.

7. Werk AN, Cascorbi I. Functional gene variants of CYP3A4. Clin PharmacolTher. 2014; 96: 340-8.

8. Nagai K, Ono H, Matsuura M, Hann M, Ueda S, et al. Progressive renal insufficiency related to ALK inhibitor, alectinib. Oxf Med Case Reports. 2018; 2018: 009.

9. Shimada M, Fukuda M, Fukuda M, Kitazaki T, Hashiguchi K, et al. Adverse renal effects of anaplastic lymphoma kinase inhibitors and the response to alectinib of an ALK+ lung cancer patient with renal dysfunction. Onco Targets Ther. 2017; 10: 3211-3214.

10. Ramachandran P, Morcus R, Tahir M, Onukogu I, Spinowitz B, et al. Alectinib (Alecensa)-induced reversible grade IV nephrotoxicity: a case report and review of the literature. J Med Case Rep. 2018; 12: 303.

11. Caravaca-Fontán F, Fernández-Juárez G, Praga M. Acute kidney injury in interstitial nephritis. CurrOpin Crit Care. 2019; 25: 558-564.

12. Praga M, Sevillano A, Auñón P, González E. Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. Nephrol Dial Transplant. 2015; 30: 1472-9.

13. Raghavan R, Shawar S. Mechanisms of Drug-Induced Interstitial Nephritis. Adv Chronic Kidney Dis. 2017; 24: 64-71.

14. Troxell ML, Higgins JP, Kambham N. Antineoplastic Treatment and Renal Injury: An Update on Renal Pathology Due to Cytotoxic and Targeted Therapies. Adv AnatPathol. 2016; 23: 310-29.

15. Brosnan EM, Weickhardt AJ, Lu X, Maxon DA, Barón AE, et al. Druginduced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib. Cancer. 2014; 120: 664-74.

16. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014; 15: 1119-28.

17. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. A method for estimating the probability of adverse drug reactions. Clin PharmacolTher. 1981; 30: 239-45.