


CASE REPORT

Pharmacokinetics of alectinib and its metabolite M4 in a patient with advanced lung adenocarcinoma undergoing hemodialysis: A case report

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Abstract

This study presents the first detailed pharmacokinetic data of alectinib and its metabolite M4 in a patient with anaplastic lymphoma kinase (ALK)-rearranged lung adenocarcinoma undergoing hemodialysis. When the patient was administered a daily 300 mg bid dose of alectinib, the maximal observed plasma concentration (C_{max}) of alectinib and M4 were 638 and 82 ng/ml, respectively, at steady-state (day 9). These pharmacokinetic data were similar to those previously reported in patients with normal organ function. The trough plasma concentration (C_{trough}) of alectinib and M4 on the hemodialysis day were 562 and 66 ng/ml, respectively, identical to those on post-hemodialysis day. He remains well and in partial remission 12 months after his diagnosis. We believe that alectinib is feasible and effective for patients with ALK-rearranged non-small cell lung cancer undergoing hemodialysis.

KEYWORDS

alectinib, ALK rearrangement, lung cancer, M4, pharmacokinetics

INTRODUCTION

Renal impairment (RI) associated with suboptimal efficacy or significant toxicity of anticancer agents due to altered pharmacokinetics (PK) is not uncommon in non-small cell lung cancer (NSCLC) patients.¹ Therefore, cancer management in RI patients is a major clinical challenge.

Alectinib is recommended as the preferred first-line therapy for patients with advanced NSCLC harboring an anaplastic lymphoma kinase (ALK) fusion gene.² A population PK analysis revealed that alectinib dose adjustment is unnecessary in patients with mild to moderate RI.³ However, PK of alectinib has not previously been studied in patients with severe RI, despite publication of a case report in which the effectiveness and safety of alectinib with 300 mg twice-daily dose in a patient undergoing hemodialysis (HD) was demonstrated.⁴ Thus, understanding the effects of HD on the PK of alectinib is crucial for ensuring efficacy and minimizing adverse effects in these patients. Here, we present the first-ever PK data from a patient with advanced NSCLC on maintenance HD treated with alectinib.

CASE REPORT

A 55-year-old male ex-smoker with HD-dependent RI due to diabetic nephropathy for 9 years was admitted to the hospital for assessment of a right neck mass. The initial demographic features and hemodialysis information are shown in supplemental Table S1. Computed tomography (CT) of the chest revealed a 3.5-cm mass in the right upper lobe and multiple enlarged mediastinal lymph nodes (Figure 1a–b) and ^{F-18}fluorodeoxyglucose (FDG)-positron emission tomography revealed abnormally increased FDG accumulation in the right upper lung, supraclavicular and mediastinal lymph nodes, liver, and brain (Figure 1e). The patient was eventually diagnosed with advanced lung adenocarcinoma (cT2aN3M1c) having ALK-rearrangement detected by the Ventana ALK (D5F3) immunohistochemistry assay. Gamma knife radiosurgery was performed for metastatic brain lesions (Figure 1c, d) and alectinib 300 mg twice-daily was initiated considering the report of Suzuki et al.⁴

Based on the previous analysis³ revealing that plasma concentrations of alectinib and its metabolite M4 reached a

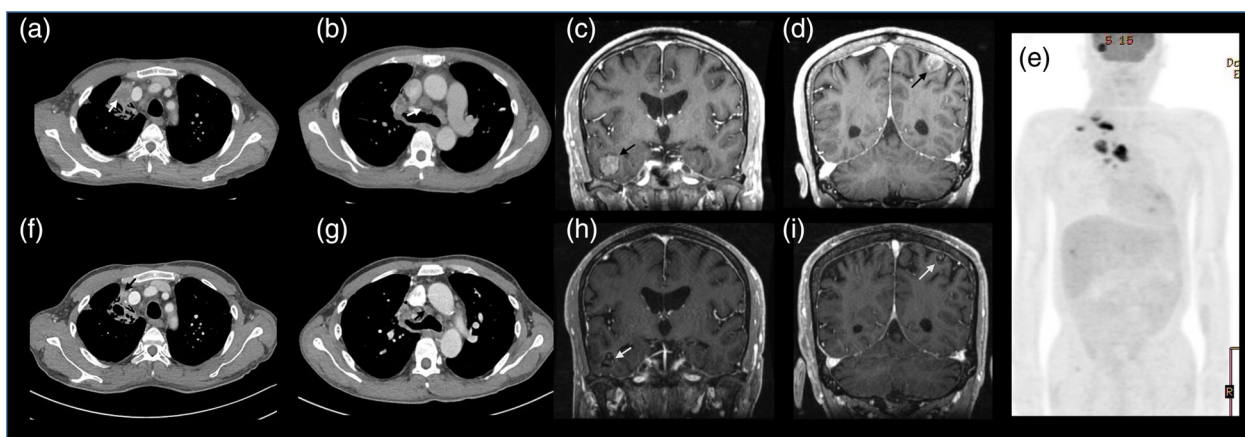


FIGURE 1 Imaging findings. (a, b) Computed tomography (CT) of the chest revealed a 3.5cm mass in the right upper lobe and multiple enlarged mediastinal lymph nodes (white arrows). (c, d) Brain magnetic resonance imaging (MRI) revealed two enhancing round masses at the right temporal and left parietal lobes (black arrows). (e) ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography revealed abnormally increased FDG accumulation in the right upper lung, supraclavicular and mediastinal lymph nodes, liver, and brain. (f–i) Decreased size of mediastinal lymph nodes as well as metastatic brain lesions was revealed by follow-up chest CT (black arrows) and brain MRI (white arrows) taken two months after alectinib initiation

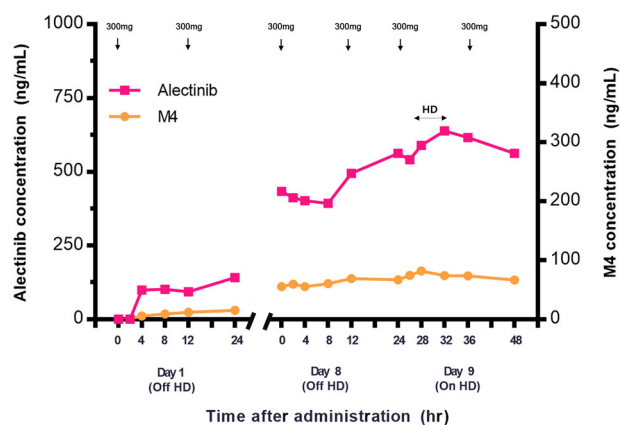


FIGURE 2 Plasma concentration-time plots of alectinib and M4 on day 1 (off HD), day 8 (off HD), and day 9 (on HD) in a patient with lung adenocarcinoma. Alectinib 300 mg was administered every 12 h. HD, hemodialysis

steady-state by day 7, we performed PK analyses of alectinib and M4 on day 1 (off HD), day 8 (off HD), and day 9 (on HD) after initiating 300 mg daily twice dose of alectinib. Blood samples were obtained before administration of alectinib, and then 2, 4, 8, 12, and 24 h after the administration on the respective day.

We determined plasma concentrations of alectinib and M4 using a validated liquid chromatography-mass spectrometric assay in the Clinical Pharmacology Research Center Laboratory of Kyungpook National University Hospital (KNUH). The patient provided written informed consent and the study protocols were approved by the Institutional Review Board of KNUH.

On day 1, the maximal observed plasma concentration (C_{\max}) of alectinib and M4 were 101 (at 8 h) and 12 ng/ml (at 12 h), respectively (Figure 2). On day 8, C_{\max} and trough plasma concentration (C_{trough}) of alectinib were

494 (at 12 h) and 433 ng/ml, respectively. Based on previous results,³ the C_{\max} on day 8 was probably earlier than this sample time (12 h). Additionally, C_{\max} and C_{trough} of M4 on day 8 were 69 (at 12 h) and 55 ng/ml, respectively.

On day 9 (on HD), C_{\max} and C_{trough} of alectinib were 638 (8 h) and 562 ng/ml. The C_{trough} of alectinib and M4 on post-HD day 10 were 562 and 66 ng/ml, which were completely similar to the respective values of day 9. Thus, PK parameters on HD-day were similar to those on non-HD days although more samples at different time points would be required to further investigate any difference.

After 5 weeks of treatment, the patient complained of general weakness and lightheadedness, and his laboratory tests revealed severe anemia (hemoglobin: 7.6 g/dl). Alectinib was suspected to be the cause of the anemia because there was no sign of bleeding. Anemia was restored after red blood cell transfusion following the discontinuation of alectinib for 1 week, and retreatment with alectinib was well tolerated without additional safety concerns. Follow-up imaging studies conducted 2 months after alectinib initiation revealed a partial response by RECIST criteria (Figure 1f–i). For the past 12 months, the patient has been receiving alectinib with no indication of disease progression and no clinically significant adverse events.

DISCUSSION

In this study, detailed PK data for alectinib and M4 during HD has been reported. In the AF-001JP study,⁵ conducted in Asian patients, C_{\max} and C_{trough} of alectinib were 528 ± 138 and 425 ± 150 ng/ml, respectively, at a steady-state after being treated with alectinib 300 mg twice-daily. Results of our PK analysis on the steady-state were similar to the AF-001JP study, revealing that alectinib and M4 remained at appropriate concentrations without significant accumulation, even in patients with severe RI. Because

alectinib is metabolized by the hepatic enzyme cytochrome P450 3A4 and alectinib and M4 are mainly excreted through the fecal route, RI may not have affected drug concentrations.³ Furthermore, C_{\max} of alectinib and M4 were not lower on HD day compared to the non-HD day, and C_{trough} of alectinib remained constant after HD. Because more than 99% of alectinib and M4 bind to plasma proteins,³ it can be inferred that alectinib and M4 were not eliminated by the dialysis membrane and additional doses may not be required for patients undergoing HD.

Alectinib 600 mg twice-daily is a globally recommended dose, with up to two dose reductions permitted in patients with severe hepatic impairment or who are unable to tolerate the full dose of alectinib.³ In this patient, alectinib at one-half of the recommended starting dose resulted in a good partial response and was not advanced to the standard full dose.

Finally, we did not evaluate whether the unbound alectinib concentrations were influenced by reduced albumin binding affinity or accumulated endogenous substrates due to reduced renal clearance in this patient.⁶ Although PK data of total alectinib in this patient undergoing HD were shown to be similar with those with normal renal function, unbound drug concentrations might be changed. Thus, these patients treated with alectinib should be carefully monitored for drug toxicity. Further studies are warranted to elucidate the PK and pharmacodynamics of alectinib in patients with severe RI.

In conclusion, this first PK data of alectinib evaluated in a patient undergoing HD will provide preliminary evidence for the feasibility of alectinib 300 mg twice-daily treatment in patients with ALK-rearranged advanced NSCLC undergoing HD.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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