



Clinical pharmacist participation in selecting and dosing targeted drugs for a patient with ALK-positive non-small cell lung cancer: a case report

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Abstract: Ceritinib and alectinib are recommended as the second-line therapies in the 2019 Chinese Society of Clinical Oncology (CSCO) guidelines for patients with anaplastic lymphoma kinase (ALK) positive non-small-cell lung cancer (NSCLC) in whom the first-line therapy has failed, but no optimal second-line treatment has been identified. Before 2018, the approved dose of ceritinib in the United States and many other countries was 750 mg/d fasted. In China, the approved dose was 450 mg/d fed although the dose of 750 mg/d fasted is still used in clinical practices. In our current case, a clinical pharmacist was involved in the selection and dose adjustment of a targeted drug for an ALK-positive NSCLC patient. The selection of second-line targeted drugs is based mainly on the results of clinical trials and real-world data of ceritinib and alectinib, along with the comprehensive analysis of health insurance policy, pharmacoeconomics, and drug accessibility. Alectinib may be more efficacious than ceritinib in second-line settings. However, in our current case, the patient finally chose ceritinib after considering the drug prices and the health insurance policy. The clinical pharmacist optimized the dosage of ceritinib from 750 mg/d fasted to 450 mg/d fed, which not only improved the patient's medication compliance but also ensured the safety and efficacy of the drug; in addition, it lowered the financial burden of both the health insurance system and the patient, offering a good example for rational drug use and health insurance cost reduction. In conclusion, in choosing second-line targeted therapy for ALK-rearranged NSCLC, a variety of factors should be considered, including clinical efficacy, adverse effects, health insurance policy, drug price, and drug accessibility, and the dosage of ceritinib should be optimized to 450 mg/d fed in real-world settings.

Keywords: Non-small cell lung cancer; ALK-positive; dose adjustment; ceritinib; case report

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Introduction

As the leading cause of cancer-related morbidity and mortality, primary lung cancer is a major public health concern in China. According to the data released by the National Cancer Center of China, lung cancer was the largest contributor to new cancer diagnoses (733,000 new

cases) and cancer-related death (610,000 deaths) in 2015 (1). Approximately 3% to 7% of lung tumors harbor anaplastic lymphoma kinase (ALK) fusions. Currently, 3 drugs, including crizotinib, ceritinib, and alectinib, have been approved in China for treating ALK-positive lung cancer. Whether ceritinib or alectinib should be selected as the

second-line targeted therapy for patients with ALK-positive non-small-cell lung cancer (NSCLC) in whom the first-line therapy has failed remains controversial and unclear.

Based on clinical trials and real-world studies, we analyzed the drug selection and dosing issues from the perspective of pharmacoeconomics, health insurance policies, and drug accessibility, with an attempt to inform the selection of second-line targeted drugs for ALK-positive NSCLC patients. Before 2018, the approved dose of crizotinib in the United States and many other countries was 750 mg/d fasted. In China, the approved dose was 450 mg/d fed although the dose of 750 mg/d fasted is still used in clinical practices. Therefore, according to the results of a few of the latest clinical trials and the drug package inserts, a clinical pharmacist recommended the adjustment of the dose of crizotinib to a patient with lung adenocarcinoma, which improved the efficacy and safety of the clinical use of crizotinib while lowering the financial burden to the health insurance system and the patient.

We present the following article in accordance with the CARE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-3853>).

Case presentation

The patient was a 38-year-old male with right lung adenocarcinoma for more than 2 years. He was admitted to our hospital in December 2019 with a cough with a little sputum, which was accompanied by occasional blood-tinged sputum. He had no other medical history or family history of tumor. He had a history of smoking for more than 20 years. The tumor was classified as a T₄N₂M_{1c} stage IV_B malignancy with ALK fusion. ALK rearrangement was detected by immunohistochemistry. The patient visited another hospital in January 2018, where the pleural fluid analysis revealed a large number of NSCLC cells. Genetic testing in January 2018 suggested ALK gene mutation. On January 17, 2018, a DP (docetaxel 130 mg/m² and cisplatin 130 mg/m²) regimen was administered. The chemotherapy course was smooth without significant adverse effects. From February 2018 to January 2019, first-line targeted therapy was conducted with crizotinib (250 mg bid). In January 2019, the patient developed grade 3 gastrointestinal adverse reactions due to crizotinib, and the dose of crizotinib was adjusted to 250 mg qd until December 2019 (*Figure 1*). He was admitted into

the department of oncology in our center in December 2019 for further diagnosis and treatment. The diagnoses at admission were as follows: (I) bronchial or pulmonary malignancy (right lung adenocarcinoma T₄N₂M_{1c} stage IV_B, ALK-positive), (II) secondary pleural malignancy, (III) secondary malignant tumors in multiple lymph nodes (right hilum and armpit), (IV) secondary mediastinal malignancy, and (V) malignant pleural effusion.

After admission, auxiliary examinations were undertaken. Chest computed tomography (CT) revealed tumor progression, while genetic testing still suggested the presence of ALK fusion. Since the patient had been taking the first-generation ALK inhibitor crizotinib for 22 months, the use of a second-generation ALK inhibitor was considered to avoid crizotinib resistance. According to the 2020 National Comprehensive Cancer Network (NCCN) guidelines and the 2019 Chinese Society of Clinical Oncology (CSCO) guidelines, second-line treatment with alectinib or ceritinib is recommended after failure of first-line treatment with crizotinib (class 2a recommendation). The patient then consulted a clinical pharmacist to determine which of ceritinib or alectinib was the better option. The clinical pharmacist offered advice to the patient based on clinical trial results, drug prices, health insurance policies, and drug accessibility. The clinician and the patient finally settled on ceritinib for the targeted therapy, and the dose initially prescribed by the clinician was 750 mg/d fasted. Based on the results of latest clinical trials and drug package inserts, the clinical pharmacist recommended that the dose of ceritinib be adjusted to 450 mg/d fed, which was adopted by the clinician. This modification ensured the safety, efficacy, and economy of the clinical use of ceritinib. During the 6-month follow-up, the patient had been consistently taking ceritinib 450 mg/d fed, with good medication compliance. He experienced mild tolerable gastrointestinal reactions during the medication period, but no serious gastrointestinal adverse reactions occurred. Imaging examinations revealed the disease was stable.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

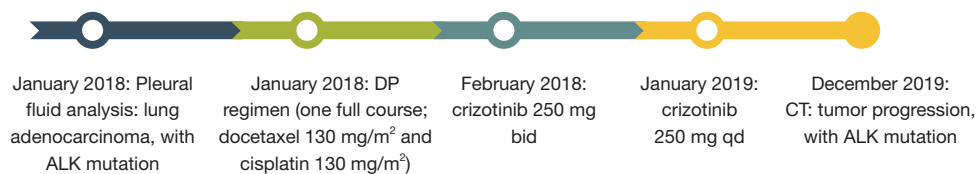


Figure 1 Timeline of diagnosis and treatment of a patient with ALK-positive non-small cell lung cancer.

Discussion

The choice between alectinib and ceritinib for second-line targeted therapy

Despite a high response rate of 60% in ALK-rearranged NSCLC, most patients develop resistance to crizotinib, typically within 1 to 2 years. Seven different acquired resistance mutations have been identified among crizotinib-resistant patients. The most frequently identified secondary mutations are L1196M and G1269A (2). However after progression on the first-line ALK TKI, ceritinib and alectinib have demonstrated efficacy against crizotinib-resistant tumours in patients with ALK-rearranged NSCLC.

In our current case, the clinical pharmacist made a suggestion on drug selection after analyzing factors including efficacy, drug prices, and health insurance policies. No head-to-head clinical study has compared the efficacy of alectinib with that of ceritinib. The clinical pharmacist reviewed the relevant clinical studies in the package inserts. In a global phase I/II single-arm, multicenter study on alectinib (NP28673), alectinib treatment achieved a progression-free survival (PFS) of 8.9 months (3) and an overall survival (OS) of 27.8 months (4) in patients with ALK-positive locally advanced or metastatic NSCLC previously treated with crizotinib. The ASCEND-5 study of ceritinib (750 mg/d fasted) enrolled patients with ALK-positive locally advanced or metastatic NSCLC previously treated with crizotinib, yielding a PFS of 5.4 months and an OS of 18.1 months (5). Thus, alectinib offers greater PFS than does ceritinib. However, due to the lack of head-to-head comparison between alectinib and ceritinib, these PFS and OS data were only informative and need to be further validated through evidence-based approaches. Davies *et al.* (6) compared the efficacies of ceritinib and alectinib after crizotinib failure by using data obtained from clinical trials and a real-world database. Indeed, real-world studies can complement clinical trial evidence for which head-to-head clinical studies are not available. After propensity score matching, alectinib had a significantly prolonged median OS

(alectinib 24.3 months; ceritinib 15.6 months). However, the dosage of ceritinib in this comparison was 750 mg/d fasted, while the approved dosage of ceritinib in China is 450 mg/d fed. Thus, more clinical studies are warranted to further analyze the efficacies of these 2 dosages in second-line settings. According to a systematic review and network meta-analysis of ALK inhibitors, on overall survival, alectinib was significantly better than crizotinib, with no other statistically significant differences between the other ALK inhibitors. Ceritinib was associated with fewer serious adverse events compared with crizotinib, there were no other statistically significant differences between crizotinib and alectinib or between ceritinib and alectinib (7). The therapeutic landscape of ALK-positive NSCLC is rapidly evolving and second-generation ALK TKIs have now become established first-line treatment. After progression on a second-generation ALK TKI, emerging data from studies of the third-generation ALK inhibitor lorlatinib have shown promise.

Drug price and medical insurance policy are also important factors when considering drug choice. Alectinib became payable by medical insurance in January 2020; however, the patient was discharged in December 2019. If he had wanted to use alectinib, he would have had to pay for it out of his own pocket. The price of alectinib is ¥49,980 Chinese yuan/month. In contrast, ceritinib was already covered by the medical insurance, at a price of ¥17,820 Chinese yuan/month. Therefore, this patient could benefit from both ceritinib and alectinib in the second-line setting after the failure of first-line crizotinib treatment; however, the difference in the efficacy of these 2 drugs remains unclear. According to a cost-effectiveness of alectinib for patients with untreated ALK-positive NSCLC in China: alectinib could prolong the mean time of progression-free and delay the time to central nervous system progression. However, because of its high drug cost, alectinib was unlikely to be cost-effective for untreated ALK-positive NSCLC patients in China (8). After considering factors of affordability, drug accessibility, and health insurance policy, both the clinician and the patient finally chose ceritinib for

second-line targeted therapy.

In our current case, the selection of second-line targeted drugs for the patient with ALK-positive NSCLC was based mainly on the results of clinical trials and real-world data of ceritinib and alectinib, along with the comprehensive analysis of health insurance policy, pharmacoeconomics, and drug accessibility. However, some limitations should be considered when interpreting this case. A comparison of efficacy between ceritinib and alectinib still lacks evidence from large clinical trials. Although findings from different clinical studies and real-world data exist, the evidence levels are low and need to be verified in clinical trials. Moreover, as the price of ceritinib in health insurance may change, so may drug selection, health insurance policies, and the evidence from more recent clinical studies. Therefore, the patient is being consistently followed up, and his dosing regimen will be adjusted if necessary.

During the COVID-19 epidemic, Hospital pharmacists prepare a list of appropriate use of medications, potential drug interactions, adverse drug reactions, and contraindications. Hospital pharmacists can continue their clinical services for the patient through telephone in order to avoid the contact of the patient to the hospitals. The patients with fever within 72 hours are recommended to go to the fever clinic of the local general hospital for diagnosis and investigation. Ceritinib can cause gastrointestinal adverse reactions. Monitor and manage patients using standard of care, including antidiarrheals, antiemetics, or fluid replacement if severe or intolerable, withhold if not responsive to antiemetics or antidiarrheals. Ceritinib can cause hepatotoxicity, monitor with liver laboratory tests, including ALT, AST, and total bilirubin, once a month.

Dose adjustment for ceritinib

Ceritinib, 750 mg/d fasted, was approved by the US Food and Drug Administration (FDA) immediately after its phase I trial was completed. However, this drug was associated with a high incidence of gastrointestinal events. Approximately 60% of patients required dose adjustments or treatment interruptions or delays due to toxic side effects (5), which can result in poor medication compliance. The ASCEND-8 explored the administration pattern and dosage of ceritinib and found ceritinib 450 mg/d fed had similar pharmacokinetic profiles to 750 mg/d fed, but with significantly improved gastrointestinal events and better efficacy (9). Data from a real-world study (10) showed that ceritinib 450 mg/d fed demonstrated superior OR, disease

control rate (DCR), and PFS in Chinese patients with brain metastases from ALK-positive NSCLC compared with a dose of 750 mg/d fasted, and therefore the approved dose for ceritinib in China is 450 mg/d.

In this case, the clinician still prescribed a dose of 750 mg/d, which was initially approved in other countries. Based on the latest drug package inserts and relevant clinical trials, the clinical pharmacist suggested changing the dosage of ceritinib from 750 mg/d fasted to 450 mg/d fed, which was adopted by the clinician. For the patient, the medical cost savings were ¥396 Chinese yuan per day and ¥11,880 Chinese yuan per month. From the pharmacoeconomics perspective, such an adjustment dramatically lowered the economic burden to the health insurance system and to the patient. From the pharmacodynamics perspective, 450 mg/d fed is superior to 750 mg/d fasted and improves the medication compliance without causing severe gastrointestinal events. Our current case also informs the rational use of ceritinib.

The patient in this case appreciated the contribution of the clinical pharmacist in drug selection and dose adjustment, and this pharmacy service not only reduced the economic burden to the patient but also reduced the occurrence of adverse gastrointestinal reactions. The clinicians and pharmacists are expected to provide timely updates to this patient on the latest clinical study results and new health insurance policies related to second-generation ALK inhibitors during follow-up visits. Metastatic central nervous system disease is present in approximately 50% of patients with ALK-positive NSCLC. Crizotinib has poor CNS penetration, however, alectinib achieves higher concentrations in the brain, demonstrated significantly prolonged CNS PFS in the phase III ALEX trial. Mildly symptomatic patients may still be considered for treatment with second-generation ALK TKI given the expected rapidity of response if close monitoring is ensured after multidisciplinary discussion. Patients with large volume or symptomatic CNS involvement should receive loco-regional treatments (either stereotactic radiosurgery or whole-brain radiation therapy) (2).

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-3853>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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