Alectinib Dose Escalation Reinduces Central Nervous System Responses in Patients with Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer Relapsing on Standard Dose Alectinib

Justin F. Gainor, MD, Andrew S. Chi, MD, PhD, Jennifer Logan, NP, MS, Ranliang Hu, MD, Kevin S. Oh, MD, Priscilla K. Brastianos, MD, Helen A. Shih, MD, Alice T. Shaw, MD, PhD

ABSTRACT

The central nervous system (CNS) is an important and increasingly recognized site of treatment failure in anaplastic lymphoma kinase (ALK)-positive, non–small cell lung cancer (NSCLC) patients receiving ALK inhibitors. In this report, we describe two ALK-positive patients who experienced initial improvements in CNS metastases on standard dose alectinib (600 mg twice daily), but who subsequently experienced recurrences with symptomatic leptomeningeal metastases. Both patients were dose-escalated to alectinib 900 mg twice daily, resulting in repeat clinical and radiographic responses. Our results suggest that dose intensification of alectinib may be necessary to overcome incomplete ALK inhibition in the CNS and prolong the durability of responses in patients with CNS metastases, particularly those with leptomeningeal carcinomatosis.

Keywords: Alectinib; ALK; Anaplastic lymphoma kinase; Leptomeningeal metastases

Introduction

Central nervous system (CNS) metastases are frequent complications of anaplastic lymphoma kinase (ALK)-positive lung cancer, affecting nearly 30% of newly diagnosed metastatic patients. Among ALK-positive patients treated with the ALK inhibitor crizotinib, the CNS is a common site of relapse. Among crizotinib-resistant patients enrolling in clinical trials of second-generation ALK inhibitors, the frequency of CNS metastases is approximately 60%. Recently, it has also been observed that such relapses may include leptomeningeal and intramedullary metastases. Together, these complications are major causes of morbidity and mortality for patients with ALK-positive non–small cell lung cancer (NSCLC).

Alectinib is a second-generation ALK inhibitor that has shown significant antitumor activity in patients with ALK-positive NSCLC. In a phase I study conducted in the United States, alectinib was associated with an objective response rate (ORR) of 55% in patients who had been previously treated with crizotinib. Similar antitumor activity was observed in a recent global phase II study of alectinib. Among 122 patients with crizotinib-resistant, ALK-positive NSCLC, alectinib produced an ORR of 50%
and median progression-free survival of 8.9 months. Alectinib has also shown impressive activity in patients with CNS metastases, including intracranial objective response rates of 42.9% to 52%. Importantly, alectinib has also produced responses in patients with leptomeningeal disease—a clinical feature that historically portends a dismal prognosis in NSCLC (median overall survival, ~12 weeks). Based upon these encouraging early results, alectinib has been granted breakthrough therapy designation by the US Food and Drug Administration for patients with ALK-positive NSCLC who have been previously treated with crizotinib.

**Case 1**

We previously reported the case of a 56-year-old man with metastatic, ALK-positive NSCLC that was complicated by leptomeningeal metastases. He received sequential treatment with crizotinib, the second-generation ALK inhibitor ceritinib, and whole brain radiation therapy (WBRT), but subsequently recurred with leptomeningeal metastases (Fig. 1A). Thereafter, he began alectinib, achieving a rapid clinical and radiographic response (Fig. 1B). Six months after starting alectinib, however, the patient developed recurrent word-finding difficulties, gait imbalance, and progressive fatigue. Repeat neuroimaging revealed patchy, diffuse intramedullary enhancement in the thoracic spinal cord and enhancement along the surface of the cervical and thoracic cord, consistent with progressive leptomeningeal carcinomatosis (Fig. 1C). Given the absence of alternative effective treatments, the patient was dose-escalated from 600 mg to 900 mg alectinib twice daily. Within several weeks, he experienced significant improvements in balance, cognition, and speech. A repeat magnetic resonance imaging (MRI) scan of his spine performed two months later showed interval improvement in intramedullary enhancement. Alectinib was well tolerated for a total of six months, at which time he was found to have asymptomatic progression in the leptomeninges. Alectinib was well tolerated.

![Figure 1. Sagittal T1-weighted postgadolinium magnetic resonance imaging scans of the thoracic spine of a patient with anaplastic lymphoma kinase-positive non-small cell lung cancer who was treated with alectinib. (A) Leptomeningeal enhancement along the surface of the thoracic spinal cord (red arrow) and an intramedullary metastasis at the level of T11 (blue arrow) before alectinib treatment. (B) Interval improvement in leptomeningeal enhancement and resolution of an intramedullary T11 metastasis after two months of alectinib 600 mg twice daily. (C) Worsening intramedullary enhancement (red arrow) in the thoracic spinal cord after six months of alectinib (600 mg twice daily). (D) Interval improvement in intramedullary enhancement in the thoracic spinal cord after dose escalation of alectinib to 900 mg twice daily.](image-url)
tolerated at the higher dose (900 mg twice daily) with only one noted side effect (grade 1 constipation).

**Case 2**

Case 2 involves a 34-year-old man with ALK-rearranged NSCLC complicated by brain and osseous metastases at the time of initial diagnosis. After completion of WBRT and palliative radiotherapy to the right ilium, the patient began first-line crizotinib. He remained on crizotinib for approximately two years, during which time he underwent a craniotomy with metastatectomy and palliative radiotherapy to several painful osseous metastases. In December 2013, he discontinued crizotinib and began carboplatin and pemetrexed. After two cycles of chemotherapy, treatment was interrupted for stereotactic radiosurgery to four brain metastases.

In July 2014, the patient enrolled on a phase I/II trial of alectinib (NCT01871805). He responded systemically to a dose of 600 mg twice daily. In May 2015, however, the patient was hospitalized with headaches and confusion and was found to be in nonconvulsive, status epilepticus. A MRI scan of his brain at that time revealed interval development of new focal leptomeningeal enhancement at multiple sites (Fig. 2A), consistent with CNS progression. The patient was started on corticosteroids and began carboplatin and pemetrexed. After two cycles of chemotherapy, treatment was interrupted for stereotactic radiosurgery to four brain metastases.

The patient has remained on alectinib 900 mg twice daily for 3.5 months with an ongoing response. In general, dose-escalated alectinib was well tolerated. Adverse events related to alectinib included transient grade 3 hypophosphatemia and grade 1 fatigue, constipation, and dyspepsia.

**Discussion**

Historically, dosing of targeted therapies in oncology has typically followed a one size fits all approach, with dose reductions for toxicities. However, there is precedent for dose-escalation strategies after treatment failure. For example, in patients with chronic myeloid leukemia, imatinib dose escalation was a common treatment approach in patients progressing on therapy before the development of second-generation BCR-ABL inhibitors. Similarly, imatinib dose escalation has also been explored at the time of disease progression in patients with gastrointestinal stromal tumors. In patients with NSCLC, “pulsatile” dosing of the epidermal growth factor receptor (EGFR) inhibitor erlotinib has been investigated in EGFR-mutant patients with leptomeningeal metastases based upon concerns for inadequate CNS penetration with standard dosing. This strategy, either alone or in combination with low-dose daily erlotinib, has demonstrated activity in EGFR-mutant patients with CNS metastases.

Similar to the experience with pulsed-dose erlotinib, the two cases outlined above show the potential...
importance of dose intensification of alectinib in patients with ALK-positive disease affecting certain sanctuary sites, such as the CNS. In a phase I dose-finding study of alectinib that was conducted in the United States, a maximum tolerated dose was not identified. Ultimately, a recommended phase 2 dose (RP2D) of 600 mg twice daily was selected based upon combined safety, efficacy, and pharmacokinetic data. However, doses up to 900 mg twice daily were also explored. Notably, alectinib 900 mg twice daily was associated with numerically higher peak concentrations and exposure levels over time compared to the RP2D. Specifically, at a dose of 900 mg twice daily, the mean (± SD) maximal plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC_{0-10}) were 1140 ± 448 ng/mL and 9840 ± 4620 ng × hr/mL, respectively. By contrast, at the RP2D of 600 mg twice daily, the mean Cmax and AUC_{0-10} were 676 ± 186 ng/mL and 5400 ± 1400 ng × hr/mL, respectively. Among 13 patients treated in the 900 mg twice daily cohort in this phase 1 trial, dose-limiting toxicities (DLTs) were reported in two patients. DLTs included grade 3 headache and grade 3 neutropenia requiring a dose delay of 7 days. Both patients remained on study, and each DLT resolved after dose reduction. Of note, among the two patients detailed in our report above, alectinib 900 mg twice daily was generally well-tolerated with no significant adverse events.

In animal models, alectinib produces relatively high brain:plasma ratios, ranging from 0.63 to 0.94. Clinically, measurable concentrations of alectinib have also been detected in cerebrospinal fluid (CSF) samples obtained from ALK-positive patients who were treated with alectinib. For example, in the report by Gadgeel et al., five ALK-positive patients with CNS metastases had paired CSF and plasma samples available for analysis, revealing an apparent linear correlation between concentrations of free alectinib in the CSF and serum. Nonetheless, CNS concentrations of alectinib did not appear fully equivalent to systemic drug levels in the above studies. Our report reinforces these observations and suggests that inadequate ALK inhibition by alectinib may still underlie CNS disease progression in some patients.

Notably, despite a clinical and radiographic repeat response to dose-escalated alectinib in case 1, the patient ultimately developed disease progression after six months. In addition to pharmacokinetic considerations, various molecular mechanisms of resistance to ALK inhibitors have been described. In particular, several ALK resistance mutations (e.g., G1202R, V1180L, and 1117I missense mutations) have been shown to confer resistance to alectinib. In case 1, however, the patient experienced CNS-only progression. We were unable to obtain a second biopsy specimen to evaluate for ALK resistance mutations or other molecular mechanisms of resistance. Moving forward, emerging technologies that allow for the detection of cell-free DNA in the circulation or CSF may provide insights into molecular mechanisms of resistance in such cases. In time, this may also inform therapeutic decision making including the relative roles of additional systemic therapy versus radiotherapy for CNS disease.

In summary, our findings suggest that dose intensification of alectinib may be helpful in prolonging the durability of responses in patients with CNS metastases, particularly those with leptomeningeal metastases. Additional investigation of this strategy may be warranted.

References