Lorlatinib Salvages CNS Relapse in an ALK-Positive Non–Small-Cell Lung Cancer Patient Previously Treated With Crizotinib and High-Dose Brigatinib

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Clinical Practice Points

- To our knowledge, this is the first detailed case of an anaplastic lymphoma kinase (ALK)-positive patient with central nervous system (CNS) disease who experienced clinical benefit with lorlatinib after disease progression during treatment with high-dose brigatinib.
- The efficacy of lorlatinib might reflect activity against an interval change in the biology of ALK-positive CNS disease occurring after initial brigatinib benefit that was not able to be suppressed by brigatinib.

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Introduction

Anaplastic lymphoma kinase (*ALK*) rearrangements are present in approximately 5% of patients with non–small-cell lung cancer (NSCLC).[1] The resulting ALK fusion proteins represent important therapeutic targets that are sensitive to treatment with ALK tyrosine kinase inhibitors (TKIs). Crizotinib was the first ALK inhibitor approved for use in advanced ALK-positive NSCLC after showing high objective response rates (ORRs) and prolonged median progression-free survival (PFS).[1-3] Despite initial efficacy, most patients treated with crizotinib eventually experience disease progression.

The central nervous system (CNS) is a common site of disease progression during treatment with crizotinib.[4] The high incidence of CNS progression is thought to be a result of poor CNS drug penetration, more than a change in the dominant biology of the cancer.[5] Next-generation ALK inhibitors including ceritinib, alectinib, and brigatinib have since shown more effective intracranial antitumor activity, in addition to activity against a range of different crizotinib resistance mutations in *ALK* and are promising options for patients who progress either systemically or intracranially during initial therapy. The most recent of these agents to be approved by the US Food and Drug Administration (FDA) is brigatinib, licensed at a lead-in dose of 90 mg once daily for 7 days followed by 180 mg once daily thereafter.[6]

We present a case of an ALK-positive patient who developed CNS metastases during treatment with crizotinib, followed by a CNS response and then CNS disease progression during higher than licensed doses of brigatinib, who was ultimately successfully treated with the third-generation ALK inhibitor lorlatinib (PF-06463922).

Case

A 42-year-old man was diagnosed with stage IV NSCLC in December 2008 with disease sites including bilateral pulmonary nodules, mediastinal lymphadenopathy, pleural effusion, and liver lesions. A baseline magnetic resonance imaging (MRI) scan was negative for intracranial metastases. Before the confirmation of an *ALK* rearrangement he was treated with cisplatin/pemetrexed/bevacizumab; cisplatin/vinorelbine/cetuximab; erlotinib and nanoparticle albumin-bound paclitaxel/cetuximab. Subsequent ALK fluorescence in situ hybridization testing revealed an *ALK* rearrangement and he commenced crizotinib treatment within the initial phase I trial at 250 mg twice daily with good partial response to therapy. In April 2011, after 5 months of crizotinib treatment, he developed new headaches with brain MRI showing at least 20 cystic lesions indicative of metastases. He declined brain radiotherapy.

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Crizotinib was continued until June 2012, when he was found to have symptomatic progression in his chest. This prompted the transition to brigatinib within the initial phase I trial of this drug starting at 240 mg once daily in July 2012. Within months, his scans showed a complete metabolic response and brain imaging showed gradual improvements in the cystic lesions.[7]

In December 2016, after more than 4 years of brigatinib treatment, he was suspected to have had a seizure after losing consciousness while driving and treatment with levetiracetam 500 mg twice daily was started. Brain MRI at this time showed no interval new lesions. Levetiracetam was ultimately discontinued because of side effects and over the next several months he experienced 3 additional seizures and treatment with lamotrigine 100 mg twice daily and lacosamide 50 mg twice daily was started. In May 2017, he was admitted to the epilepsy monitoring unit, where he was noted to have a tonic-clonic seizure with focal onset in the right arm followed by generalized convulsions of the entire body. Repeat neuroimaging showed progressive CNS disease, particularly in the left temporal region (Figure 1A-C). His systemic disease remained quiescent. Lacosamide was increased to 250 mg twice daily and he again declined radiation treatment or neurosurgical options. Brigatinib was increased to 300 mg once daily with good tolerance but reduced back to the original dose 2 months later because of lack of CNS response (Figure 1D-F). Brigatinib was ultimately discontinued and he began lorlatinib treatment at 100 mg once daily through an expanded access program in September 2017. Repeat CNS imaging 1 month later showed a decreased size of the left temporal enhancing lesion and stable adjacent cystic changes (Figure 1G-I). Repeat imaging almost 6 months later showed continued improvement in enhancing and nonenhancing cystic lesions (Figure 1J-L).

His systemic disease continues to remain quiescent after the transition from brigatinib to lorlatinib treatment. During lorlatinib treatment his triglycerides have remained normal but his cholesterol has been elevated up to 270 mg/dL (Grade 1), and he developed Grade 1 slowing of speech.

Discussion

The high rate of CNS relapse among patients treated with crizotinib is well known. The newest of the next-generation ALK inhibitors to be approved by the FDA, brigatinib, has shown a post-crizotinib median PFS of 16.7 months at the recommended dose of 180 mg.[8] Post-crizotinib, brigatinib was also shown to have an intracranial ORR of 67% and a median intracranial PFS of 18.4 months.[8] Higher doses of brigatinib were associated with consistently better CNS efficacy (CNS ORR, 50% [95% confidence interval (CI), 30%-70%] versus 67% [95% CI, 41%-87%] with 90 mg and 180 mg regimens, respectively; CNS PFS, 9.2 months [95% CI, 7.4-12.8] and 18.4 months [95% CI, 12.6 to not reached], respectively), suggesting that increasing systemic exposure to brigatinib might drive increased CNS exposures.

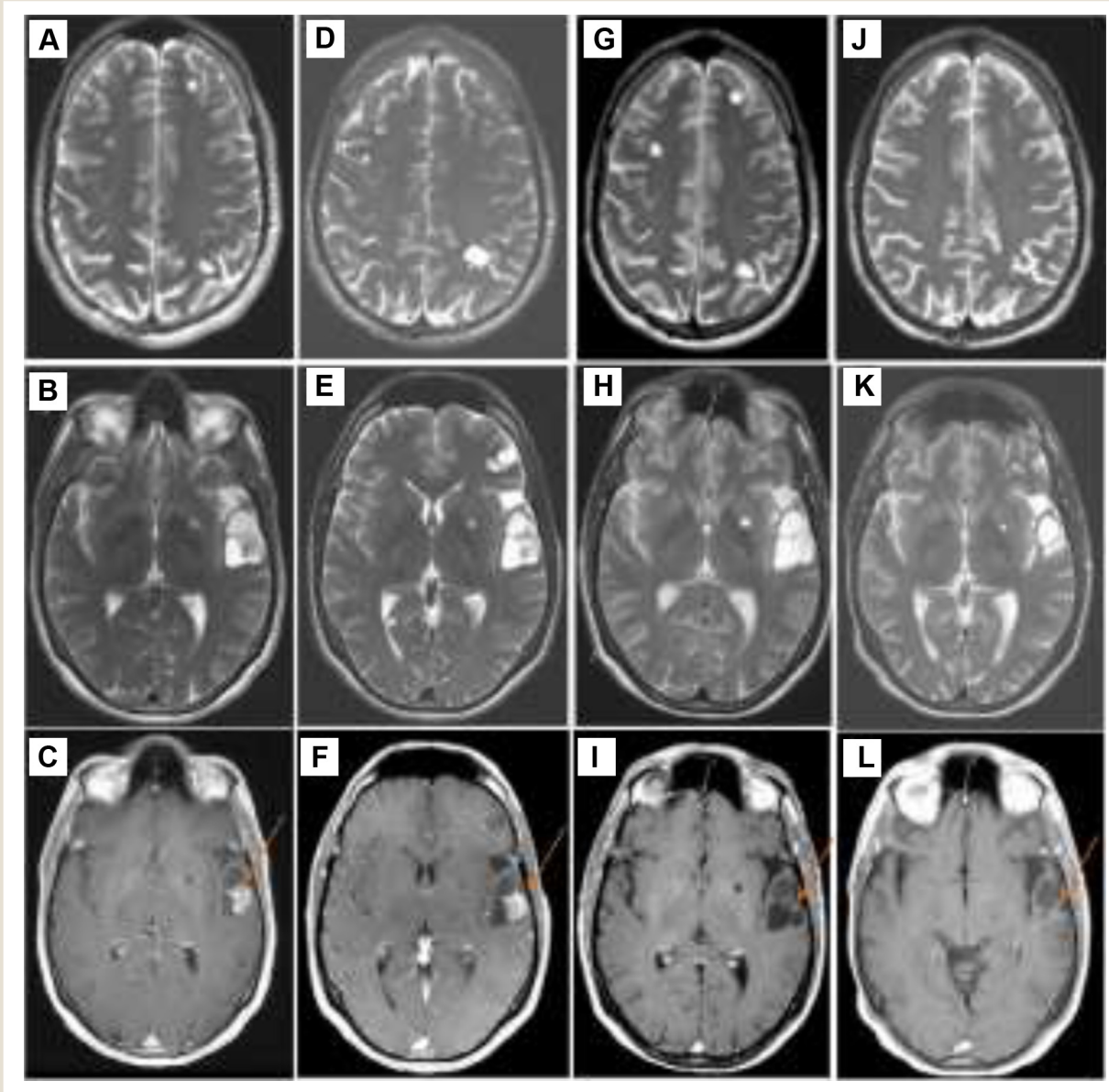
Mechanisms of acquired resistance to many of the different licensed next-generation inhibitors are now being described, some of which involve specific *ALK* kinase domain mutations.[9] Lorlatinib is a highly potent, selective ALK inhibitor that has been shown to be active against most known *ALK* kinase domain mutations and to have significant CNS penetration.[10] In a recent phase I/II study, lorlatinib showed robust clinical activity in ALK-positive patients who received treatment with at least 1 previous ALK inhibitor, most of whom were heavily pretreated and had CNS involvement.[10] Among patients who previously received 2 or more ALK inhibitors, the ORR (potentially including data on CNS and extra-CNS target lesions) was 69% with an intracranial ORR of 68%. However, this data set only included 8 patients who had received brigatinib as their most recent TKI, 3 of whom responded, with no available data on either the dose of brigatinib the patients had received or whether these responses were in the CNS and/or extra-CNS sites or disease.

Because the CNS lesions in this patient initially responded to brigatinib before progressing, inadequate penetration of brigatinib into the CNS alone cannot be the sole explanation for the later CNS progression. Instead, CNS progression during brigatinib treatment might reflect a change in the biology of the ALK-positive CNS disease, such that lorlatinib at 100 mg but not brigatinib, even at 300 mg, could overcome it within the brain. Because an ALK inhibitor alone showed activity, a second driver seems less likely and instead the growth might be explained by the emergence of a specific *ALK* mutation in the CNS. Because of the lack of systemic progression, the mutation might be one that remained sensitive to brigatinib at systemic exposures or might have only existed in the CNS, but only potentially lorlatinib's CNS concentration being higher and/or its half maximal inhibitory concentration against this mechanism being lower than with brigatinib allowed for effective suppression within the brain. For example, systemic lesions manifesting G1202R have been described as sensitive to brigatinib and a possible mechanism of acquired resistance in some patients receiving brigatinib, suggesting standard doses of brigatinib produce systemic exposures that are on the cusp for active inhibition of this mutation.[11] In some patients, systemic exposures are presumably high enough to cover this mutation and in others it is not. Consequently, even if CNS brigatinib exposures are even a little lower than systemic ones, such a mutation could emerge in the CNS. Although no CNS drug levels were assessed in this case, lorlatinib, unlike brigatinib, is not a substrate of P-glycoprotein thus is not subject to drug efflux through this mechanism and could have contributed to higher CNS exposures.[12] Assessments of circulating free DNA in cerebrospinal fluid (CSF) could conceivably be explored in the future to investigate the presence of specific CNS mutations in such situations, but unfortunately CNS-derived material from the tumor or CSF was not available in this case.

Conclusion

This case shows the potential efficacy of lorlatinib when used as CNS salvage therapy among patients progressing during brigatinib treatment, expanding the available data set of lorlatinib's activity after treatment with other next-generation ALK TKIs. The initial response to brigatinib before disease progression suggests that the subsequent intracranial antitumor activity of lorlatinib might be related to the development of an ALK-dominant resistance to brigatinib mechanism in the CNS that remained susceptible to lorlatinib either potentially because of its higher potency against the mechanism and/or greater CNS penetration of the drug.

Figure 1 Regression in Brain Metastases in an Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer Patient Treated With Lorlatinib After Brigatinib. (A-C) After 4.9 Years of Treatment With 240 mg Brigatinib (June 2017). Axial T2 (A, B) and Post-Contrast T1 (C) Imaging Showing Multiple Scattered Nonenhancing Cysts, and a Solid/Cystic Lesion Within the Left Temporal Lobe With Dominant Irregularly Enhancing Nodule Within its Posterolateral Aspect (Arrow). (D-F) After 2 Months of Treatment With 300 mg Brigatinib (August 2017). Axial T2 (D, E) and Post-Contrast T1 (F) Imaging Showing a Slight Increase in Size and Solidity of the Dominant Irregularly Enhancing Nodule and Slight Increase in Size of the Associated Cysts Despite Increase in Therapy (Arrow). (G-I) After 5 Weeks of Treatment With 100 mg Lorlatinib (November 2017). Axial T2 (G, H) and Post-Contrast T1 (I) Imaging Showing a Decrease in Size of the Enhancing Nodule, With Only Trace Residual Enhancing Remaining After Transition to lorlatinib (Arrow). Adjacent Cystic Change Is Stable Albeit With Slice Selection Differences, Whereas Cysts Scattered Elsewhere Are Stable or Incrementally Smaller. (J, K) After 5.3 Months of Treatment With 100 mg Lorlatinib (March 2018). Axial T2 (J, K) and Post-Contrast T1 (L) Imaging Showing a Substantial Decrease in Size of the Extensive Cystic Disease Throughout the Brain (Including Numerous Lesions Not Pictured) and Further Slight Decrease in Size of the Irregularly Enhancing Nodule (Arrow)



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Disclosure

The authors have stated that they have no conflicts of interest.

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