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

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Introduction

Anaplastic lymphoma kinase (ALK) rearrangements are present in approximately five percent 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 demonstrating 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 demonstrated 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 on initial therapy. The most recently FDA-approved of these agents is brigatinib, licensed at a lead-in dose of 90 mg once daily for seven days followed by 180 mg once daily thereafter.⁶

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

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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 MRI was negative for intracranial metastases. Before the confirmation of an ALK rearrangement he was treated with cisplatin/pemetrexed/bevacizumab; cisplatin/vinorelbine/cetuximab; erlotinib and abraxane/cetuximab. Subsequent ALK FISH testing revealed an ALK rearrangement and he commenced crizotinib within the initial phase I trial at 250 mg twice daily with good partial response to therapy. In April 2011, after five months on crizotinib, he developed new headaches with brain MRI demonstrating at least 20 cystic lesions suspicious for metastases. He declined brain radiotherapy. 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 demonstrated gradual improvements in the cystic lesions.⁷

In December 2016, after more than four years on brigatinib, he had a suspected seizure after losing consciousness while driving and was started on levetiracetam 500 mg twice daily. Brain MRI at this time showed no interval new lesions. Levetiracetam was ultimately discontinued due to side effects and over the next several months he experienced three additional seizures and was started on lamotrigine 100 mg twice daily and lacosamide 50 mg twice daily. 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 demonstrated 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 two months later due to lack of CNS response (Figure 1, D-F). Brigatinib was ultimately discontinued and he began lorlatinib at 100 mg once daily through an expanded access program in September 2017. Repeat CNS imaging one month later demonstrated decreased size of the left temporal enhancing lesion and stable adjacent cystic changes (Figure 1, G-I). Repeat imaging almost six months later demonstrated continued improvement in both enhancing and non-enhancing cystic lesions (Figure 1, J-L).

His systemic disease continues to remain quiescent after the transition from brigatinib to lorlatinib. On lorlatinib 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, brigatinib, has demonstrated a post-crizotinib median PFS of 16.7 months at the recommended dose of 180 mg.⁸ Post-crizotinib, brigatinib was also found to have an intracranial ORR of 67% and a median

intracranial PFS of 18.4 months⁸. Higher doses of brigatinib were associated with consistently better CNS efficacy (CNS ORR 50% [95% CI, 30% to 70%] vs. 67% [95% CI, 41% to 87%] with 90 mg and 180 mg regimen, respectively; CNS PFS 9.2 months [95% CI, 7.4 to 12.8] and 18.4 months [95% CI, 12.6 to not reached], respectively), suggesting that increasing systemic exposure to brigatinib may 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 at least one prior ALK-inhibitor, most of whom were heavily pretreated and had CNS involvement¹⁰. Among patients who received two or more prior ALK inhibitors, the ORR (potentially including data on both CNS and extra-CNS target lesions) was 69% with an intracranial ORR of 68%. However, this dataset 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 CNS and/or extraCNS sites or disease.

As the CNS lesions in this case 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, the CNS progression on brigatinib may reflect a change in the biology of the ALK-positive CNS disease, such that lorlatinib at 100mg but not brigatinib, even at 300 mg, could overcome it within the brain. As an ALK inhibitor alone demonstrated activity, a second driver seems less likely and instead the growth may be explained by the emergence of a specific ALK mutation in the CNS. Given the lack of systemic progression, the mutation may be one that remained sensitive to brigatinib at systemic exposures or may have only existed in the CNS, but only potentially lorlatinib's CNS concentration being higher and/or its half maximal inhibitory concentration (IC50) 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 both sensitive to brigatinib and a possible mechanism of acquired resistance in some patients on 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. While no CNS drug levels were assessed in this case, lorlatinib, unlike brigatinib, is not a substrate of P-glycoprotein (PgP) 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 demonstrates the potential efficacy of lorlatinib when used as CNS salvage therapy among patients progressing on brigatinib, expanding the available dataset of lorlatinib's activity post other next generation ALK TKIs. The initial response to brigatinib prior to disease progression suggests that the subsequent intracranial antitumor activity of lorlatinib may be related to the development of an ALK-dominant resistance mechanism to brigatinib in the CNS that remained susceptible to lorlatinib either potentially due to its higher potency against the mechanism and/or greater CNS penetration of the drug.

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Clinical Practice Points

- To our knowledge, this is the first detailed case of an ALK-positive patient with CNS disease who experienced clinical benefit on lorlatinib after disease progression on high-dose brigatinib.
- The efficacy of lorlatinib may reflect activity against an interval change in the biology of the ALK-positive CNS disease occurring after initial brigatinib benefit that was not able to be suppressed by brigatinib.

Figure 1.

Regression in brain metastases in ALK-positive NSCLC patient treated with lorlatinib after brigatinib.

A-C: After 4.9 years on 240 mg brigatinib (June 2017). Axial T2 (A, B) and post-contrast T1 (C) imaging demonstrating multiple scattered non enhancing 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 on 300 mg brigatinib (August 2017). Axial T2 (D, E) and post-contrast T1 (F) imaging demonstrating 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 on 100 mg lorlatinib (November 2017). Axial T2 (G, H) and post-contrast T1 (I) imaging demonstrating decrease in size of the enhancing nodule, with only trace residual enhancing remaining after transition to lorlatinib (arrow). Adjacent cystic change is stable given slice selection differences, while cysts scattered elsewhere are stable or incrementally smaller.

J-K: After 5.3 months on 100 mg lorlatinib (March 2018). Axial T2 (J, K) and post-contrast T1 (L) imaging demonstrating 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).