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Intra-cranial efficacy of brigatinib in an *ALK*-positive non-small cell lung cancer patient presenting leptomeningeal carcinomatosis

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ABSTRACT

Objectives: Brigatinib is a second-generation ALK inhibitor which demonstrated activity over crizotinib-resistance, especially on brain metastasis by increased blood-brain penetration. However, its activity on leptomeningeal disease is unknown and scarcely reported.
Materials and methods: We hereby report the case of lepto-meningeal disease in crizotinib- and ceretinib- treated patient who was successfully treated by brigatinib.
Results: The patient achieved intracranial response to brigatinib more than 14 months.
Conclusion: Our case provides additional data on brigatinib's intracranial activity, not only on brain metastasis but also on leptomeningeal disease, after experiencing resistance to both crizotinib and ceretinib, 1st and 2nd generation ALK inhibitors.

1. Introduction

Survivals of advanced anaplastic lymphoma kinase (*ALK*-positive) non-small cell lung cancer (NSCLC) patients have dramatically changed since the development of efficient ALK tyrosine kinase inhibitors (TKi). However, *ALK*-positive patients seem to relapse more commonly in the central nervous system (CNS), considered as a sanctuary site. Whether brain metastases (BM) or lepto-meningeal disease (LMD), both are associated with very poor prognosis [1]. Though there is evidence of intracranial activity of 1st generation ALK TKi - crizontib to 2nd and next-generations TKi alectinib, ceretinib against BM, few cases report their activity on LMD. We present the case of a patient who developed LMD under crizotinib and ceritinib and achieved intracranial response > 14 months, with brigatinib, a second-generation ALK TKi, given under expanded access program.

2. Case presentation

A 51-year-old Caucasian man, ECOG 0, former smoker of 30 pack-years, was diagnosed with advanced lung adenocarcinoma T2N2M1c with bone and liver metastasis. immunohistochemistry (IHC) detected ALK expression alone. FISH was not performed due to lack of material.

He was started on crizotinib in December 2015 and achieved a 10-month progression-free survival (PFS). In October 2016, he presented with mild confusion. Brain MRI confirmed intra-cranial relapse with multiple parenchymal lesions and diffused leptomeningeal enhancement, whereas cerebrospinal fluid cytology did not find malignant cells. Body-scanner showed extra-cranial stable disease. He was started on ceritinib at 750 mg/d. However, three months later, the patient worsened neurologically. Imagery revealed parenchymal and leptomeningeal progression, without extra-cranial involvement. Thus, platin-based chemotherapy with bevacizumab was prescribed resulting in a partial response after 4 cycles. During maintenance regimen, a follow-up CT-scan revealed local thoracic relapse on the right lower lobe. Brain MRI demonstrated stable intra-cranial disease, with parenchymal and leptomeningeal enhancement (Fig. 1A). Lung biopsy for updated mutational status showed ALK 2 + IHC staining and negativity by FISH. Additional NGS testing on lung tissue and plasma samples did not find resistance mutations to ALK inhibitors. After multi-disciplinary discussion, brigatinib was started under expanded access program, in July 2017, at 180 mg once daily with a 7-day lead-in period at 90 mg. After 2 months treatment, the patient showed neurological signs of improvement. Brain MRI (Fig. 1B) and CT-scan evaluation showed both intra- and extra-cranial favorable response, which is currently maintained,

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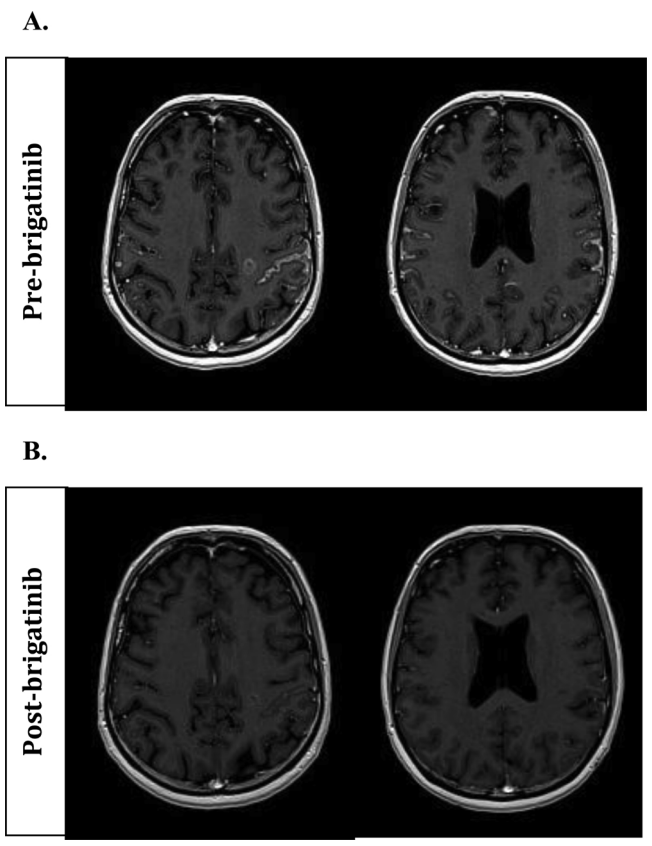

Fig. 1. Axial magnetic resonance imaging (MRI) of the brain. A. Before brigatinib, in January 2017, showing multiple intra-axial brain metastases associated with leptomeningeal enhancement. B. After 2 months of brigatinib, patient showing partial intracranial response with marked regression of leptomeningeal and parenchymal enhancement.

more than 14 months from drug-initiation. The drug is well tolerated and quality of life significantly improved.

3. Discussion

Brigatinib (AP26113) is a second-generation ALK TKi, with a broader spectra of activity, specifically on acquired resistance mutations [2]. Brigatinib has demonstrated significant improvement of PFS and response rate (RR), both in crizotinib-refractory *ALK*-positive NSCLC patients [3] (Phase II ALTA trial) and in 1st line treatment [4] (Phase III ALTA-1 L Trial), compared with the 1st ALK-TKi crizotinib. Consequently, it received FDA approval in crizotinib-pretreated patients in April 2017.

Furthermore, recent studies also suggested the benefit of brigatinib against BM in crizotinib-refractory *ALK*-positive patients [5,6]. In the phase II ALTA trial, patients in the arm B (patients receiving 180 mg daily with a 7-day lead-in at 90 mg; n = 18) showed intracranial objective response rate (IC ORR) up to 67%. Considering all patients with CNS involvement at baseline, the median CNS PFS was of 18.4 months. IC ORRs were similar in subsets without prior radiation or progression post-radiation.

Similarly, in ALK inhibitor naïve patients, brigatinib also suggested intracranial efficacy [4]. In the ALTA-1 L trial, 90/275 patients had BM at baseline. Among them, 39 had measurable BM. The IC ORR was of 78% (95% CI, 52–94) against 29% (95% CI, 11–52) with crizotinib. The 12-month survival rate was estimated at 67% in the brigatinib group against 21% in the crizotinib group.

Leptomeningeal disease (LMD) is distinct from BM as its incidence is less frequent in *ALK*-positive NSCLC patients and is associated with

Table 1
Literature review: published case reports on leptomeningeal disease (LMD) in NSCLC patients treated with brigatinib.

Case	Authors	Age, sex	Chemotherapy received	Previous ALK-inhibitors received	CNS involvement	Dose of brigatinib	Duration of treatment of brigatinib
#1	Geraud et al. JTO (2018)	43 y, female	Yes	ceritinib	Parenchymal and meningeal	90 mg/d increased to 180 mg/d	9 months
#2	Geraud et al. JTO (2018)	54 y, female	No	crizotinib, ceritinib	Parenchymal and leptomeningeal	90 mg/d increased to 180 mg/d	7 months
#3	Current case	51 y, male	Yes	crizotinib, ceritinib	Parenchymal and leptomeningeal	90 mg/d increased to 180 mg/d	> 14 months

poorer prognosis [1]. The efficacy of next-generation ALK inhibitors is less known as patients with LMD have often been excluded from trials. Some reported cases have been published on the efficacy of other ALK TKi, such as alectinib, on leptomeningeal carcinomatosis [7,8]. Yet, for brigatinib, they remain few with a distance of 9 months for the best [9]. In addition with our latest case, emerging facts suggest brigatinib's durable intra-cranial activity in BM as well as LM in *ALK*-positive NSCLC patients (Table 1).

4. Conclusion

To conclude, we reported the first case of successful prolonged intra-cranial response to brigatinib in a patient with *ALK*-positive advanced lung adenocarcinoma presenting with leptomeningeal disease, with initial poor prognosis. Our case provides additional data to support brigatinib intra-cranial efficiency over 1st and 2nd generation ALK-TKIs, including in LMD setting.

Disclosures

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