Integration of ceritinib and bevacizumab as a promising treatment strategy for brain metastases from ALK mutation-position non-small cell lung cancer: a case report

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ABSTRACT

Ceritinib shows efficacy in ALK[+] NSCLC patients with BM. However, the disease will inevitably progress over time due to acquired resistance. We now report a case with BM from advanced lung adenocarcinoma with ALK mutations who exhibited a surprising and long-term response to treatment of ceritinib combined with bevacizumab.

Abbreviations: NSCLC= non-small cell lung cancer, ALK= anaplastic lymphoma kinase, BM= Brain metastases, CT= computed tomography, SD= stable disease , CR= complete response, VEGF= vascular endothelial growth factor, PFS= progression-

free survival ， TTIR= time to intracranial tumor response, EGFR-TKIs= epidermal growth factor receptor tyrosine kinase inhibitor

Keywords: Non-small cell lung cancer
Brain metastases
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ALK mutation

INTRODUCTION

Brain metastases(BM) is a severe and common complication of non-small cell lung cancer (NSCLC)and it significantly deteriorates the prognosis of these patients[1]. Patients with gene rearrangement in the anaplastic lymphoma kinase (ALK) gene are known to have a higher risk of brain metastases. CNS metastases occur in approximately 20% to 30% of patients with ALK mutation-positive NSCLC when diagnosed[2].

Ceritinib, a second-generation anaplastic lymphoma kinase (ALK) inhibitor, shows better efficacy than traditional chemotherapy drugs and first-generation ALK-I crizotinib in ALK+NSCLC patients with BM due to higher brain-to-blood exposure (AUCinf) ratio and lower IC50. Thus ceritinib is widely used in clinical treatment. However, the acquired resistance of ceritinib is an urgent problem for patients[3]. Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor(VEGF) that is known to play a pivotal role in tumor-associated angiogenesis[4].

CASE REPORT

In August 2013, a 47-year-old Chinese man was found to have an ALK mutation-positive lung adenocarcinoma, stage IIIA T1aN2M0 (based on the Seventh edition of the TNM classification for lung), during the bronchoscopy in Shanghai Chest Hospital. An enhanced computed tomography (CT) (Fig 1) revealed an enlargement of hilar lymph node, swollen lymph nodes with multiple fusion and pulmonary lymphangitic carcinomatosis. According to the physical status, the patient received 6 cycles treatment of pemetrexed and radiotherapy and then he had achieved stable disease (SD).

In December 2013, CT revealed the lesions still existed and remained active in enhanced images (Fig 2) in our hospital. Therefore, the patient underwent oral crizotinib (250mg twice daily) treatment in February 2014. After 2 months, chest CT scan images demonstrated the disease got a complete response (CR) (Fig 3), and he was continuing with crizotinib.

About 21 months later (November 2015) the patient's condition worsened and brain metastases were discovered (Fig 4). Subsequently, the patient underwent stereotactic radiosurgery (Gamma Knife, 18Gy - 36Gy) that resulted in a 4-months stabilization with subsequent relapse of intracranial lesions (Fig 5). In March 2016, the patient underwent stereotactic radiosurgery for lesions (Cyber Knife, 14Gy × 2F) in Beijing 307 Hospital.

However, in January 2018, the patient was diagnosed with stage ⅢB, T3N2M0 (based on the Eighth edition of AJCC) primary bowel cancer. The patient underwent resection surgery (right hemi-colon and part of the small intestine with size - 4.5×0.5 cm) and received chemotherapy of the XELOX project (capecitabine and oxaliplatin) as adjuvant therapy. The pathological report showed serous cell adenocarcinoma of protrude type accompanied by signet-ring cell carcinoma, which invading into intestinal muscularis and nerves, surgical margins (-), per-intestinal lymph nodes 6/20 (+), with immunohistochemistry (IHC): CDX2 (+), Villin (+), Ck7 (-), TTF-1 (-), NapsinA (-).

In October 2018, with the progression in the intracranial lesions (Fig 6), the patient developed symptoms of numb in hands and damage of vision. He was prescribed with ceritinib (orally 450mg daily with meals) because of the patient's strong refusal of the third stereotactic radiosurgery in 3 years. Bevacizumab (300mg one times) was also added to this therapy to relieve brain edema. Surprisingly, the combination of ceritinib and bevacizumab obtained a significant curative effect and the patient got CR in just 1 month(Fig 7) and progression-free survival (PFS) lasting 25 months until January 2021.

DISCUSSION

Arm1 of the ASCEND-7 trial (NCT02336451) evaluated the efficacy and safety of oral ceritinib in patients with metastases in the brain without evidence of

leptomeningeal carcinomatosis (LC), previously treated with radiation to the brain and with prior exposure to an Anaplastic lymphoma kinase inhibitor (ALK-I). The investigators determined the median time to intracranial tumor response (TTIR) was 1.87 months (95% CI: 1.7-7.5 months) and the median PFS was 7.2 months (95% CI: 3.3-10.9 months). To the best of our knowledge, our case is the first combination of ceritinib and bevacizumab and shows better efficacy which caused CR in just 1 month and PFS lasting 25 months until January 2021 in contrast to the result of the ASCEND-7.

The program that we choose ceritinib plus bevacizumab takes the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKIs) plus bevacizumab as lessons. Previous studies[5] suggested that EGFR- TKIs plus bevacizumab could significantly prolong PFS than EGFR-TKIs alone[6]. The rationale is that bevacizumab may help augment systemic and intracranial drug activity by modulating the tumor vasculature[7]. Also, bevacizumab could take control with symptoms of encephaledema or intracranial hypertension to improve the overall prognosis[8]. These points of view give us reason to Integrate ceritinib and bevacizumab.

The acquired resistance of ceritinib is an urgent problem for patients. The

mechanism involves mutations, gene amplifications (ALK-dependent),

histopathologic changes and activation of bypass tracks (ALK-independent) and so on[9]. Knowledge-based sequential treatment with first-, second- and third-

generation ALK inhibitors is a significant strategy, while combination of ALK and other pathway inhibitors is another promising option aiming at this problem[9]. Such as the VEGF pathway contains targets of bevacizumab means potentially bevacizumab and ALK inhibitors may achieve clinical benefits[10].

On the other hand, re-induction of VEGF and subsequent VEGF-dependent tumor growth is suggested as one of the major mechanisms of acquired resistance to EGFR-TKI[11]. Likewise, we suspect that the ceritinib resistance mechanism may have connection with VEGF and further studies are required to better elucidate the mechanisms between them.

CONCLUSION

It is possible to integrate ceritinib and bevacizumab provides a method to prevent ceritinib resistance and a more promising treatment strategy for patients with BMs from NSCLC with ALK mutations. This case suggests a synergic effect of the combination therapy, and further accumulation of cases and formal clinical trials are expected. Besides, we hope our idea of analogical reasoning from EGFR-TKIs medication regimen gives a prompt to clinical doctors.

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CONFLICTS OF INTEREST

This research has no conflict of interests.

ETHICAL APPROVAL

The article describes a case report. Therefore, no additional

permission from our Ethics Committee was required.

AUTHOR CONTRIBUTIONS

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