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Clinical lasting response of crizotinib in ALK positive lung squamous cell carcinoma with brain metastasis

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Summary. Anaplastic lymphoma kinase (ALK) gene-rearrangement in non-small-cell lung cancer (NSCLC) was first reported in 2007 (1). EML4-ALK oncogene fusion is the most common form and has been identified in 2-5% patients with NSCLC, especially adenocarcinoma (2-5). It has defined a molecular subgroup of NSCLC that is susceptible to targeted kinase inhibition. Crizotinib, a specific ALK inhibitor, has shown marked clinical response to ALK rearranged NSCLC (6, 7), but it has been reported its poor blood brain barrier penetration (8). How about the efficacy and safety of crizotinib in NSCLC with brain metastases? How to treat brain metastasis patients with ALK sensitive mutation? What could be the best therapeutic strategy, ALK inhibitor, radiotherapy, chemotherapy or combination? This case shows that second line of crizotinib is effective against advanced squamous cell carcinoma (SCC) with brain metastases carrying EML4-ALK oncogene fusion.

Key words: ALK, squamous cell carcinoma, brain metastases, crizotinib

Case presentation and follow-up

A 37-year-old Chinese male, severe smoker was diagnosed with stage IV (cT1bN3M1ab) squamous cell carcinoma (SCC) of the right upper lung with brain and contralateral lobe metastasis. Three months after first-line chemotherapy of gemcitabine with cisplatin, the patient showed evidence of progressive disease, with an increase in the size and number of both pulmonary and brain metastases. A second round trans-bronchial tumor biopsy revealed a positive EML4-ALK rearrangement (break-apart fluorescent in situ hybridization analysis). As a second-line treatment, crizotinib was administered orally at a dose of 250 mg twice per day. Marked tumor regression became apparent 1 week later. Both pulmonary and brain metastases became regressed and this response persisted for more than 18 months. In this study, we present a case of crizotinib long lasting responsive pulmonary and brain metastases in EML4-ALK rearranged SCC without local radiotherapy. The potential explanation for efficacy of crizotinib is brain metastases tumor tissue distribution and blood brain barrier disruption by chemotherapy. It is also possible crizotinib may accumulate in brain metastases. However, whether crizotinib actually enters into brain metastases and the concentration in CSF has not been adequately elucidated. Another question is about the therapeutic choice between crizotinib and local radiotherapy. Further confirmatory studies are still needed to clarify the efficacy and safety of crizotinib plus radiotherapy in ALK positive NSCLC patients with brain metastases.

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Discussion

Oncogenic ALK fusion genes are present in a subgroup of NSCLC, and the ALK inhibitor responsive patients are usually have a history of never or light smoking and with adenocarcinomas (9, 10). However, in the present case, the patient is severe smoker with SCC. Thus, it may indicate that these characteristics alone were inadequate to predict which patients would have a response to crizotinib.

The brain is a common site of advanced NSCLC; brain metastases are found in approximately 20-40% of all patients and are associated with poor prognosis (11, 12). The control and prevention of brain metastases have emerged as important and challenging therapeutic issues. Crizotinib is an oral inhibitor of ALK, c-MET, ROS1 (13, 14). It has been demonstrated that overall survival for patients with advanced ALK-positive NSCLC was significantly longer in the patients given either first- or second-line crizotinib when compared with conventional chemotherapy (6, 7). However, the cerebrospinal fluid (CSF) drug levels of crizotinib remain low, which implies poor blood-brain barrier penetration (8). Such a phenomenon seems to be self-contradictory with the clinical effect in brain metastases.

Just like others oral TKIs, including erlotinib (15), and gefitinib (16), crizotinib have a low CSF-to-plasma ratio (8). However, crizotinib was associated with systemic and intracranial disease control in patients with ALK rearranged NSCLC with brain metastases. A majority of patients on the initial trial of crizotinib with untreated or previously treated brain metastases had long periods of systemic disease control without brain metastases progression. The systemic disease control rate (DCR) at 12 weeks was 63%; the intracranial DCR was 56%. Among patients with previously treated brain metastases, the systemic DCR was 65%, the intracranial DCR was 62% (17). It demonstrates the efficacy and safety of TKI on the control of brain metastases (13, 17).

Two cases of crizotinib-responsive brain metastases in ALK-rearranged NSCLC have been reported (18, 19). In both cases, radiotherapy was performed before crizotinib treatment. It may suggest that brain radiotherapy affect CSF drug levels by disrupting the blood brain barrier. However, in the present case, the patient hasn't received any radiotherapy. A potential explanation is brain metastases tumor tissue distribution and blood brain barrier disruption by chemotherapy. In mouse xenograft model, the tissue concentration of gefitinib is higher than that in plasma and CSF (20). It has been demonstrated that erlotinib accumulated in brain metastases (21). Because ALK positive NSCLCs respond to the crizotinib in a similar fashion, it is possible crizotinib may accumulate in brain metastases. However, whether crizotinib actually enters into brain metastases has not been adequately elucidated. And the measurements of CSF and tumor tissue concentrations of the drug have not been fully investigated. The effectiveness of crizotinib in brain metastases is still required to further clarification.

Another question is about the therapeutic choice between crizotinib and local radiotherapy. It has been demonstrated that combined first-line EGFR TKI therapy and radiotherapy for advanced NSCLC patients are more effective (22, 23). WBRT and EGFR-TKIs might be more beneficial than EGFR-TKIs alone (22). Use of SBRT with erlotinib as a second- or subsequent line therapy resulted in high PFS and OS (24). Initial progression of TKI-treated cancers occurred predominantly in original disease sites. Consolidation SBRT was judged feasible in a subset of patients following maximum TKI response and may have prevented oligo-progression. Further confirmatory studies are still needed to clarify the efficacy and safety of crizotinib plus radiotherapy in ALK positive NSCLC patients with brain metastases. Whether crizotinib might enhance radio-sensitivity or not, the optimal time to add radiotherapy to crizotinib treatment, are still need further study.

Conclusion

We present a case of durable response of ALK rearranged SCC with pulmonary and brain metastases to crizotinib without radiotherapy. The potential explanation for efficacy of crizotinib is brain metastases tumor tissue distribution and blood brain barrier disruption by chemotherapy. It is also possible crizotinib may accumulate in brain metastases. However, wheth-

er crizotinib actually enters into brain metastases and the concentration in CSF has not been adequately elucidated. Another question is about the therapeutic choice between crizotinib and local radiotherapy. Further confirmatory studies are still needed to clarify the efficacy and safety of crizotinib plus radiotherapy in ALK positive NSCLC patients with brain metastases.

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