Rapid Response of Brain Metastasis to Crizotinib in a Patient with ALK Rearrangement–Positive Non–Small-Cell Lung Cancer

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CASE PRESENTATION

A 56-year-old woman who never smoked presented with left supraclavicular lymphadenopathy. A computed tomography (CT) scan revealed a lung tumor in the left upper lobe and mediastinal lymphadenopathies. Biopsy of the supraclavicular lymph node confirmed non–small-cell lung cancer (NSCLC) with a poorly differentiated tumor histology favoring adenocarcinoma. The results of a bone scan and head CT scan were negative for metastases, and the patient was considered to have T1N3M0 stage IIIB disease. She received first-line platinum-based chemotherapy concurrent with thoracic radiotherapy and achieved a complete response. Twenty months after completion of chemoradiotherapy, the patient presented with recurrent disease in the form of a brain metastasis, which was treated with γ-knife radiotherapy. However, 4 months later, a positron emission tomography–CT scan showed multiple lymph node metastases affecting mediastinal, contralateral hilar, and para-aortic lymph nodes (Fig. 1A, arrows), and a head CT scan revealed asymptomatic recurrence of brain metastasis, which was a progression of the previously identified central nervous system lesion that was treated with γ-knife radiotherapy (Fig. 2A). Mutation analysis of the biopsy of tumor tissue at diagnosis showed that the tumor was wild type for the epidermal growth factor receptor (EGFR) gene. Fluorescence in situ hybridization analysis with break-apart probes for the anaplastic lymphoma kinase (ALK) gene, however, revealed the presence of an ALK break-apart probes for the anaplastic lymphoma kinase (ALK) gene. Fluorescence in situ hybridization analysis with break-apart probes for the anaplastic lymphoma kinase (ALK) gene, however, revealed the presence of an ALK rearrangement. Crizotinib (250 mg twice daily) was administered orally with no clinically relevant adverse effects. After 3 weeks of crizotinib therapy, a repeat head CT scan showed a marked decrease in the size of the contrast-enhanced lesion in the frontal lobe and amelioration of surrounding edema (Fig. 2B). A repeat positron emission tomography–CT scan revealed that the mediastinal, contralateral hilar, and para-aortic lymphadenopathies had almost completely resolved (Fig. 1B). A follow-up CT scan of the brain performed after 11 months of crizotinib therapy showed complete resolution of the brain metastasis. The patient is currently still receiving crizotinib therapy with no evidence of progression on regular follow-up every 3 to 6 weeks.

DISCUSSION

The development of brain metastases from NSCLC is a challenging clinical problem, having an adverse impact on quality of life and survival. Given that chemotherapy is only moderately beneficial for such metastases, brain radiotherapy remains a standard palliative treatment. Crizotinib is the first ALK tyrosine kinase inhibitor to become clinically available and has shown marked and durable efficacy for the treatment of NSCLC positive for ALK rearrangement. It is considered to have a limited role in the treatment of brain metastases, however, as a result of its poor penetration of the blood–brain barrier.1,2 Indeed, the sole site of initial progressive disease is the brain in patients with ALK rearrangement–positive NSCLC treated with crizotinib. The present patient was diagnosed with ALK rearrangement–positive NSCLC and manifested pronounced and rapid regression of a brain metastasis only 3 weeks after initiation of crizotinib treatment. To our knowledge, this is the first report of a marked effect of crizotinib on a brain metastasis derived from ALK rearrangement–positive NSCLC. Crizotinib, which is also a potent inhibitor of the tyrosine kinase MET, was recently shown to induce regression of glioblastoma positive for MET amplification.3 It is thus noteworthy that crizotinib has been proven effective for the treatment of both primary and metastatic brain tumors despite its limited ability to penetrate the blood–brain barrier. Previous studies have also documented the effectiveness of EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib for the treatment of brain metastases of NSCLC positive for activating EGFR mutations, again despite the relatively low permeability of the blood–brain barrier to these drugs.4 Our present case indicates that crizotinib can be effective for the treatment of brain metastasis in a subset of patients with ALK rearrangement–positive NSCLC in a manner similar to EGFR inhibitors in patients with NSCLC positive for EGFR mutation.

The present report provides insight into the efficacy of crizotinib for the treatment of brain metastasis in crizotinib-naive patients with ALK rearrangement–positive NSCLC. Further investigation to define the clinical benefit of crizotinib...
Response of Brain Metastasis to Crizotinib

for the treatment of brain metastasis in this patient population is thus warranted.

CONSENT
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

FIGURE 1. PET-CT imaging before and after crizotinib treatment. (A) PET-CT scan before treatment revealing multiple lymph node metastases affecting mediastinal, contralateral hilar, and para-aortic lymph nodes (arrows). (B) PET-CT scan 3 weeks after initiation of crizotinib therapy showing almost complete resolution of the multiple lymph node metastases. PET-CT, positron emission tomography–computed tomography.

REFERENCES

FIGURE 2. Head CT scans before and after crizotinib treatment. (A) Head CT scan before treatment showing a single brain metastatic lesion with surrounding edema in the right frontal lobe. (B) Head CT scan 3 weeks after the initiation of crizotinib therapy revealing a marked decrease in size of the contrast-enhanced lesion and amelioration of the surrounding edema. CT, computed tomography.