Ineffectiveness of Crizotinib on Brain Metastases in Two Cases of Lung Adenocarcinoma with EML4-ALK Rearrangement

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CASE 1

A 45-year-old man was referred for progressive stage IV lung adenocarcinoma after second-line chemotherapy. He had an Eastern Cooperative Oncology Group performance status of 2 with bone pain. Chest and abdominal computed tomography (CT) showed a right pleural effusion with liver and diffuse bone metastases. Magnetic resonance imaging (MRI) of the brain revealed an asymptomatic left frontal lesion. Given the evidence of positive EML4-ALK rearrangement on the pleural biopsy (assessed by fluorescence in situ hybridization), crizotinib 250 mg twice daily was started. After 2 weeks, the patient's performance status improved to 0, with disappearance of bone pain. Six weeks after starting treatment, CT demonstrated a significant shrinkage of all tumor sites outside the central nervous system (CNS). However, an MRI performed 6 and 10 weeks after the initiation of crizotinib showed multiple new brain lesions and an increased size of the left frontal metastasis (shown in Fig. 1). The patient received whole-brain radiotherapy (WBRT) after discontinuation of crizotinib but died after 3 weeks, from progression of brain metastases.

CASE 2

A 57-year-old man with stage IV lung adenocarcinoma had progressive disease after three lines of treatment, including chemotherapy, bevacizumab, and erlotinib. Chest and abdominal CT showed pulmonary lymphangitic carcinomatosis, right pleural effusion, and peritoneal carcinomatosis. A brain MRI revealed multiple, small, diffuse asymptomatic metastases. Given the evidence from fluorescence in situ hybridization of EML4-ALK rearrangement in the initial biopsy, treatment was begun with crizotinib 250 mg twice daily. Four weeks later, chest and abdominal CT showed decreased pulmonary lymphangitic carcinomatosis, disappearance of the peritoneal effusion, and stable pleural effusion. However, the patient experienced progressive ataxia and MRI revealed an increase in the size and number of brain lesions. The patient received WBRT after discontinuation of crizotinib but died 9 weeks later from carcinomatous meningitis.

DISCUSSION

ALK-EML4 translocation is a recently discovered tyrosine kinase target present in 4% to 5% of non–small-cell lung cancers.[1] Crizotinib, an inhibitor of ALK tyrosine kinase, often produces dramatic responses in patients with ALK rearrangement, with a reported overall response rate of 55% and a 2-year overall survival of 54%.[2–4]

Resistance to crizotinib can occur through several mechanisms. These include secondary mutations in the ALK kinase domain, gain of ALK gene fusion copy number, and emergence of other oncogenic drivers.[5] The brain seems to be a common and preferential site of relapse, probably related to poor penetration of crizotinib into the CNS. Shaw et al.[4] described a patient treated with crizotinib, who presented with progressive cerebral disease, although tumor outside the CNS did not progress. The concentration of crizotinib was 0.53 µmol/liter in plasma but only 0.0014 µmol/liter in the cerebrospinal fluid.[3] This could explain the contrast seen in our two cases between disease progression in the brain, and response or stable disease in other tumor sites.

The majority of patients included in clinical trials assessing crizotinib had brain metastases that were controlled by prior treatment. More data are needed to evaluate the activity of crizotinib on brain metastases and to determine whether WBRT should be given before crizotinib in cases of untreated CNS lesions.

REFERENCES

1. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–566.
2. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–1703.
3. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011;29:e443–e445.
4. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004–1012.
5. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012;18:1472–1482.

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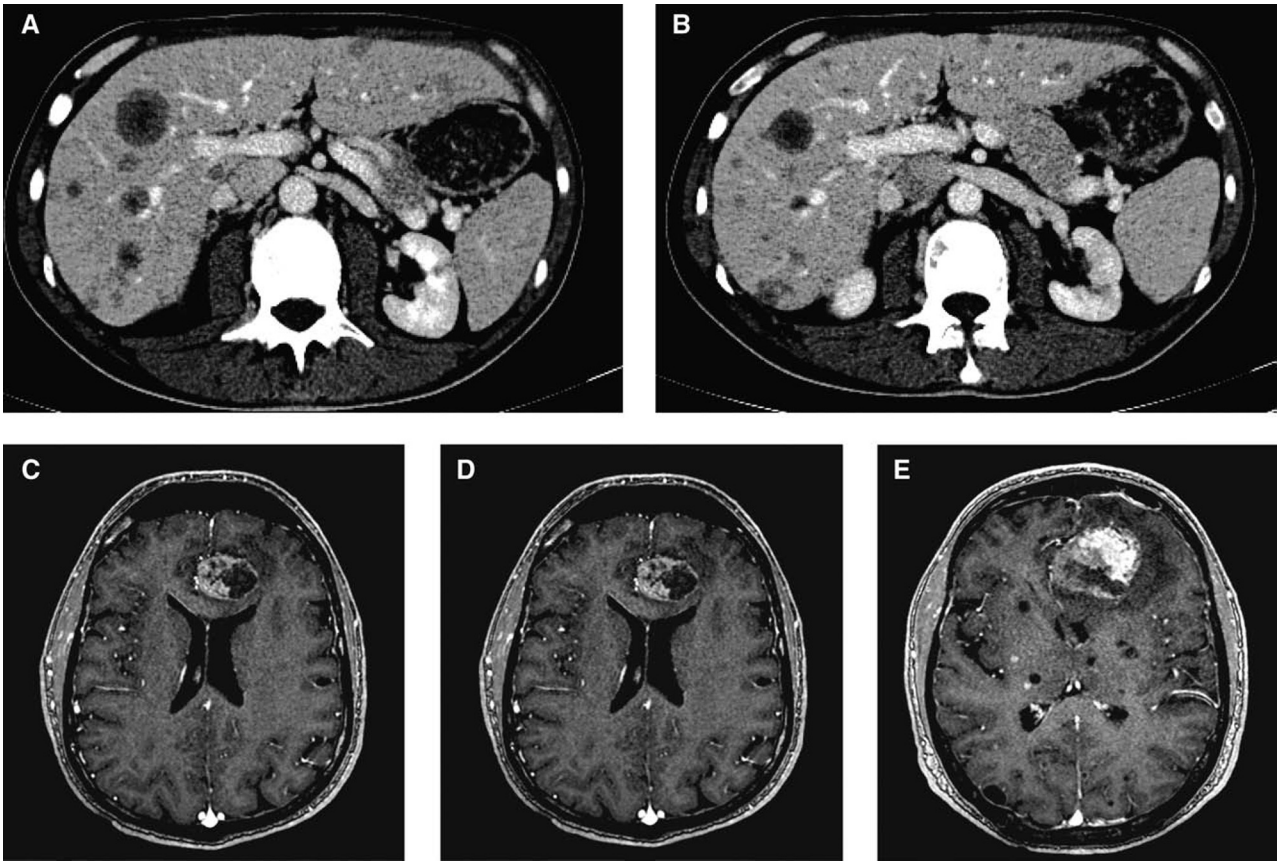

FIGURE 1. Abdominal computed tomography (*A*) before and (*B*) after 6 weeks of crizotinib showed a substantial decrease in the size of all liver metastases. *C*, *D*, and *E*, Magnetic resonance imaging T1 gadolinium at (*A*) initiation of crizotinib and after (*B*) 6 and (*C*)10 weeks of treatment showed an increase in size of the left frontal cerebral metastasis of 28 mm to 54 mm associated with the appearance of a right periventricular lesion.