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Alectinib Induces a Durable (>15 Months) Complete Response in an *ALK*-Positive Non-Small Cell Lung Cancer Patient Who Progressed on Crizotinib With Diffuse Leptomeningeal Carcinomatosis

Introduction

Crizotinib, a multitargeted anaplastic lymphoma kinase (ALK) inhibitor, has demonstrated significantly improved progression-free survival over chemotherapy in patients with advanced *ALK*-rearranged non-small cell lung cancer (NSCLC) [1, 2]. However, prolonged survival also seems to lead to eventual relapse in the sanctuary sites, presenting as leptomeningeal carcinomatosis or intramedullary metastasis, both of which have extremely poor prognoses [3]. In this paper, we described one patient who developed diffuse leptomeningeal carcinomatosis as the only "site" of progression after a prolonged response to crizotinib and who is being treated successfully with a second-generation ALK inhibitor alectinib (CH5424802/RO5424802; F. Hoffmann-La Roche AG, Basel, Switzerland, http://www.roche.com) alone. That treatment has been ongoing for >15 months.

Case Presentation

The patient is a 29-year-old Persian never-smoker woman who was diagnosed with stage IIIA NSCLC at age 22. She received curative surgical resection and adjuvant cisplatin and Navelbine (GlaxoSmithKline, Research Triangle Park, NC, http://www.gsk.com) chemotherapy. She remained free of disease for the next 3 years but then developed malignant pleural effusion and spinal metastasis. She received thoracic spine radiation and completed six cycles of carboplatin, paclitaxel, and bevacizumab chemotherapy with partial response. Three months later she was found to have at least 10 small brain lesions and received whole-brain radiation. Her tumor tested positive for rearrangement of the anaplastic lymphoma kinase (*ALK*) gene, and she was enrolled into the randomized phase III trial comparing docetaxel and pemetrexed with crizotinib (PROFILE1007, NCT00932893). She was randomized to the chemotherapy arm (docetaxel) and achieved stable disease after four cycles of docetaxel, which was stopped because of patient intolerance. Six months later she relapsed with osseous metastasis including the pelvis and received radiation to the pelvis. She then crossed over to crizotinib 250 mg twice daily in November 2011, and crizotinib was reduced to 200 mg twice daily after 2 months because of neutropenia. She achieved a complete response systematically. Eighteen months into her crizotinib treatment she developed transient double vision, but magnetic resonance imaging (MRI) performed at that time did not reveal any abnormality. Approximately 1 month later she developed right hand paresthesia, right facial numbness, and dysarthria and, with repeated MRI, was found to have leptomeningeal carcinomatosis diffusely involving the cerebellum and cervical spinal cord. She was started on Decadron (Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com) 6 mg three times a day with resolution of her symptoms while crizotinib was continued. She was urgently referred to a phase I/II trial of alectinib (RO5424802/CH5424802) (AF-002JG, NCT01588028), a second-generation ALK inhibitor, for crizotinib-resistant patients but was ineligible due to lack of measurable disease by repeated computed tomography (CT) scan of the chest, abdomen, and pelvis and steroid dependency. The AF-002JG protocol requires patient to be free of neurological symptoms while off steroids for at least 14 days prior to enrollment. She could not receive more cranial radiation because of previous whole-brain radiation. With permission from F. Hoffmann-La Roche and approval by the U.S. Food and Drug Administration and the institutional review board (IRB) of the University of California Irvine (UCI) Medical Center, she received alectinib 600 mg orally twice daily under an emergency (bypassing the mandatory 30-day waiting period) single-patient investigational new drug (IND) application in early August 2013 after signing an informed consent approved by the UCI IRB. Crizotinib was discontinued the day before initiation of alectinib. Pretreatment lumbar puncture on the same day before starting alectinib demonstrated increased monocytes, and the cerebral spinal fluid (CSF) cytology was positive for malignant adenocarcinoma (Fig. 1). However, tumor material was insufficient to perform immunohistochemistry for ALK, fluorescence in situ hybridization for *ALK* break-apart analysis, or reverse transcription polymerase chain reaction to detect potential acquired resistant *ALK* mutations. Pretreatment MRI also revealed diffuse enhancement of the meninges (Fig. 2A, 2C).

By the time of alectinib initiation, the patient had experienced significant side effects from the high dose of steroids, including oral thrush and vaginal candidiasis, despite oral fluconazole treatment; weight gain; truncal obesity; fluid retention; and insomnia. She was able to taper off Decadron after 10 days on alectinib. A lumbar puncture 14 days after starting alectinib revealed significantly decreased but persistent malignant cells. Her dysarthria symptoms returned briefly while off steroids; the dose of alectinib was increased to 750 mg twice daily, and steroids at 2 mg twice daily were reinitiated. Her leptomeningeal carcinomatosis symptoms resolved and never recurred. A repeated lumbar puncture 4 weeks after initiation of alectinib revealed clearance of malignant cells. A 6-week follow-up MRI of the brain and entire spine showed resolution of the meningeal enhancement (Fig. 2B, 2D). The patient was eventually weaned off all steroids within 2 months of alectinib and has remained asymptomatic ongoing for >15 months. A repeated CT scan of the chest, abdomen, and pelvis in November 2014 revealed continual systemic control with no evidence of visceral disease and stable bone metastasis.

Discussion

Alectinib is a second-generation ALK inhibitor that has demonstrated clinical activity against brain metastasis in patients with *ALK*-rearranged NSCLC who were ALK inhibitor naïve [4] or resistant to crizotinib [5]. From the report of the dose-finding

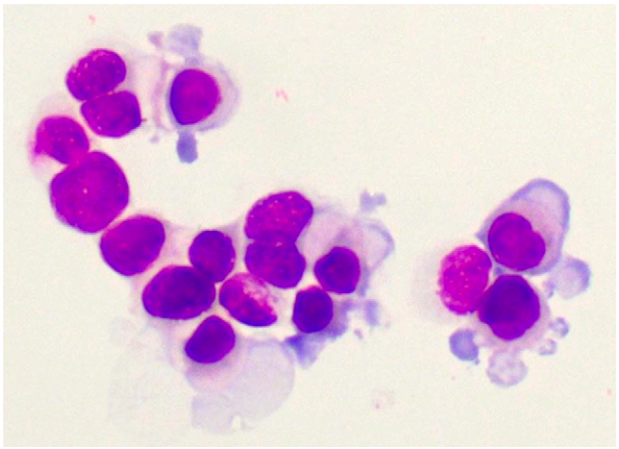

Figure 1. Malignant cells in the cerebral spinal fluid before alectinib treatment.

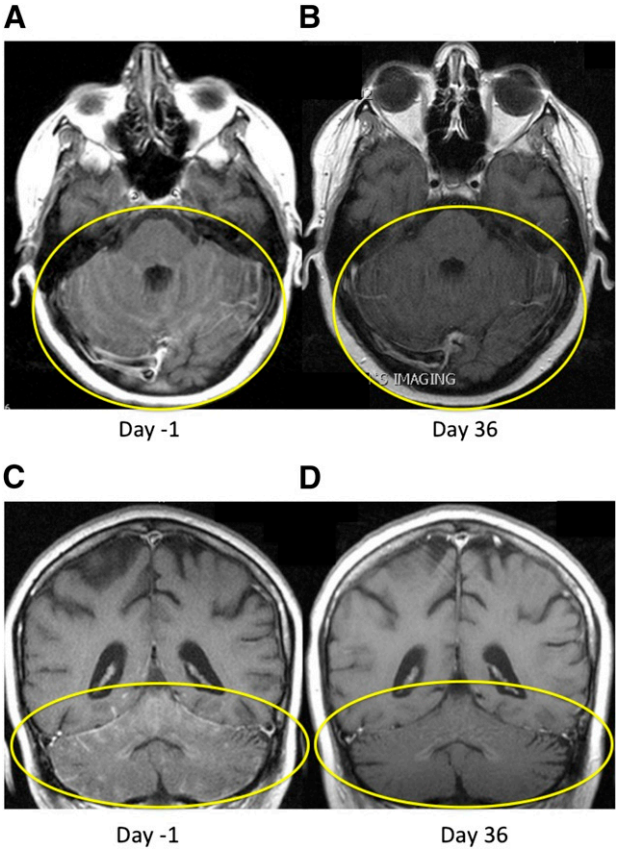

Figure 2. Images of the cerebellum before and after 6 weeks of alectinib treatment, showing resolution of the meningeal enhancement. **(A, B)**: Axial magnetic resonance imaging (MRI). **(C, D)**: Coronal MRI images of the cerebellum before and after 6 weeks of alectinib treatment showing resolution of the meningeal enhancement.

portion of the alectinib phase I/II trial conducted in the U.S. (AF-002JG, NCT01588028), an initial objective response rate of 52% in brain metastasis was observed with alectinib [4]. The recommended phase II dose for alectinib was determined to be 600 mg orally twice daily, although there was no significant difference in the serum pharmacokinectics of alectinib at 600 mg or 750 mg twice daily [5]. However, a linear correlation seems to exist between the concentrations of free (non-albumin-bound) alectinib in the CSF and in the serum, with a ratio of ~0.75 indicating a very high degree of penetration of alectinib into the CNS [5]. Consequently, when the rapid steroid taper within 2 weeks of initiating alectinib treatment did not completely eliminate the leptomeningeal carcinomatosis symptoms of our patient, we increased the dose of alectinib to 750 mg twice daily and restarted steroid treatment, followed by a prolonged but successful steroid taper (2 months). Indeed, 750 mg twice daily was well tolerated by the patient without any laboratory abnormalities, in concordance with the phase I results of the U.S. alectinib trial. However, given the potentially higher level of alectinib that is achievable in the CSF with a 750-mg twice-daily dose, the excellent leptomeningeal carcinomatosis control with alectinib in our patient may not be translatable at the 600-mg twice-daily dose, although a recent publication after submission of this case report showed that alectinib at 600 mg twice daily also had significant activity against leptomeningeal carcinomatosis in ALK-positive NSCLC patients who failed crizotinib and ceritinib [6]. Given that the patient is not on protocol treatment, no paired alectinib plasma/CSF ratio was determined.

Crizotinib has been shown to achieve a very low CSF/plasma level based on one case report of a patient with *ALK* rearrangement who also progressed on crizotinib with isolated leptomeningeal carinomatosis [7]. Progression in the central nervous system (CNS) is a leading cause of crizotinib failure [8]. Several approaches have been tried to treat leptomeningeal carcinomatosis in patients with *ALK*-rearranged NSCLC. Ahn and colleagues have combined crizotinib and intrathecal (IT) methotrexate (MTX) in treating two crizotinib-naïve patients with *ALK*-rearranged NSCLC [9]. Both patients were able to receive IT MTX for 5 months before one had symptomatic deterioration and the other developed necrotizing leukoencephalopathy from IT MTX [9]. Ceritinib, a second-generation ALK inhibitor, had been shown to be effective under compassionate use for $>$5 months at the time of the report in a crizotinib-resistant patients with *ALK*-rearranged NSCLC who developed carcinomatosis meningitis [10]. Another second-generation ALK inhibitor, AP26113, has also shown consistent CNS activity in crizotinib-resistant *ALK*-rearranged patients [11], but to date there is no report of single-agent AP26113 activity against leptomeningeal carcinomatosis arising in crizotinib-resistant patients with *ALK*-rearranged NSCLC. Other strategies that have been used to treat brain metastasis in patients with *ALK*-rearranged NSCLC, such as crizotinib with high-dose systemic chemotherapy [12], once-daily dosing instead of twice daily [13], or high-dose cirizotinib [14], have not been reported in patients with leptomeningeal carcinomatosis.

Leptomeningeal carcinomatosis seemed to be a late presentation of advanced stage IV NSCLC [3, 15]. Overall survival of NSCLC patients with leptomeningeal carcinomatosis remains poor. Consequently, leptomeningeal carcinomatosis is usually an exclusion criterion in the vast majority of NSCLC clinical trials. Even when leptomeningeal carcinomatosis is allowed, as in the AF-002JG trial, patients with leptomeningeal carcinomatosis have to be asymptomatic off all steroids for at least 2 weeks, and that is quite difficulty to achieve without any concurrent treatment because leptomeningeal carcinomatosis is usually diagnosed when patients become symptomatic. Furthermore, leptomeningeal carcinomatosis is considered nonmeasurable by Response Evaluation Criteria in Solid Tumors, making assessment of response to treatment in a clinical trial difficult. With the advent of

second-generation ALK inhibitors that have demonstrated CNS activity, the activity of these ALK inhibitors in brain metastasis including leptomeningeal carcinomatosis are being investigated systemically [16]. Meanwhile, case reports such as our current patient case and the patient case by Arrondeau et al. [10] are how we can communicate the efficacy of second-generation ALK inhibitors in leptomeningeal carcinomatosis in patients with *ALK*-rearranged NSCLC.

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Disclosures

Sai-Hong Ignatius Ou: Roche/Genentech (RF, H); **Edward B. Garon:** Merck, Bristol-Myers Squib (C/A); Merck, Genentech, AstraZeneca, Pfizer, Novartis, Puma (RF). The other authors indicated no financial relationship.

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