Alternate-day Treatment with Crizotinib for Drug-induced Esophagitis and Liver Damage in a Patient with EML4-ALK Fusion Gene-positive Lung Adenocarcinoma

Yoko Tsukita¹, Tatsuro Fukuhara¹, Maki Kobayashi¹, Mami Morita¹, Aya Suzuki¹, Kana Watanabe¹, Tetsuya Noguchi², Yasuko Kurata³, Manabu Suno⁴ and Makoto Maemondo¹

Abstract

A 44-year-old woman who was diagnosed with anaplastic lymphoma kinase-positive lung adenocarcinoma developed brain metastases, multiple spinal metastases and meningeal dissemination. Crizotinib was administered after the failure of first-line chemotherapy. Esophagitis and liver damage were induced by the twice-daily administration of crizotinib at 250 mg and 200 mg, respectively. The alternate-day administration of crizotinib (250 mg, twice daily) was able to control disease progression without any adverse effects for several months. We evaluated the relationship between the serum concentration of crizotinib and the development of esophagitis and liver damage. The alternate-day administration of crizotinib is one of the strategies for managing the severe toxicity of crizotinib.

Key words: non-small-cell lung cancer, crizotinib, ALK rearrangement, drug-induced esophagitis, alternate-day administration

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Introduction

Crizotinib is an oral tyrosine kinase inhibitor (TKI) that blocks the signals from anaplastic lymphoma kinase (ALK), mesenchymal-epithelial transition (MET), and ROS1 (1-3). ALK gene rearrangements, including the rearrangement of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene, are observed in approximately 2-5% of non-small-cell lung cancer (NSCLC) patients (4, 5). Several studies have shown the efficacy of crizotinib to be similar to that of epidermal growth factor receptor TKI (EGFR-TKI) with regard to progression free survival and response rate (6, 7). The major adverse effects of crizotinib are vision disorder, diarrhea, nausea, and vomiting. In addition, several reports have demonstrated that severe esophagitis may be induced by crizotinib (8-13). Here, we report a case of recurrent esophagitis induced by crizotinib that was successfully

managed by the alternate-day administration of crizotinib.

Case Report

A 44-year-old woman who was diagnosed with lung adenocarcinoma underwent a left lower lobectomy in February 2003 (pT1N2M0 stage IIIA). In July 2011, a brain tumor was resected from the left temporal lobe and pathologically confirmed as a metastatic tumor from lung cancer. EML4-ALK gene-fusion was detected in the metastatic brain tumor by an immunohistochemical analysis and fluorescent *in situ* hybridization. It was also subsequently detected in the surgical specimen of the primary lung cancer by an immunohistochemical analysis. No other recurrent lesions were found, thus she was indicated for observation without additional treatment. In July 2012, multiple brain metastases and meningeal dissemination appeared. The brain metastases progressed despite 3 cycles of cisplatin and pemetrexed,

¹Department of Respiratory Medicine, Miyagi Cancer Center, Japan, ²Department of Gastrointestinal Medicine, Miyagi Cancer Center, Japan, ³Department of Pharmacy, Okayama University Hospital, Japan and ⁴Center for the Development of Medical and Health Care Education, Okayama University, Japan

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Correspondence to Dr. Makoto Maemondo, maemondo-ma693@aioros.ocn.ne.jp

Figure 1. A: Esophagogastroduodenoscopy revealed erosive lesions with white coat and vesicles in the middle and lower thoracic part of the esophagus. B: Esophagitis disappeared ten days after crizotinib discontinuation.

Table. Serum Concentration of Crizotinib.

	Dose (mg/day)	Dosing interval	Dosing period (day)	Administration day or non administration day	Before or after administration	Concentration (ng/mL)
*1	500	daily	7	administration day	after	468 (peak)
*2	400	daily	15	administration day	before	212 (trough)
*3	500	alternate day	7	administration day	before	17.5 (trough)
*4	500	alternate day	29	administration day	before	52.8 (trough)

*1 Severe esophagitis developed.

*2 Liver damage appeared.

*3,4 There were no any adverse events related to crizotinib during this dosing period.

Figure 2. A: Seven months after discontinuation of the first crizotinib treatment, MRI revealed multiple spinal nodules and enhancement of the meninges. B: Two months after alternate-day administration of crizotinib at 250 mg daily, MRI showed shrinkage of the spinal nodules. C: Five months after alternate-day administration of crizotinib, MRI demonstrated regrowth of the spinal nodules.

thus she underwent whole brain radiation therapy. A second-line treatment with crizotinib (250 mg, twice daily) was started. Dysphasia and retrosternal pain developed rapidly (within one week). Esophagogastroduodenoscopy (EGD) revealed severe esophagitis in the middle and lower thoracic parts of the esophagus (Fig. 1A). The patient's serum concentration of crizotinib was 468 ng/mL at the onset of esophagitis (Table). The administration of crizotinib was discontinued, and she recovered from the symptoms after ten days. The improvement of the esophagitis was confirmed by EGD (Fig. 1B). The administration of crizotinib was resumed at a reduced dose (200 mg, twice daily), but 15 days later there was a grade 3 elevation in her alanine aminotransferase (ALT) level. The patient's serum concentration of crizotinib was 212 ng/mL (Table). The administration of crizotinib was discontinued and she was discharged after recovery from crizotinib-induced hepatic toxicity.

Seven months after discharge, she developed lower extremity weakness and dysuria. Magnetic resonance imaging (MRI) revealed the progression of multiple spinal metastases and meningeal dissemination (Fig. 2A). The reinitiation crizotinib treatment was considered necessary due to the lack of other treatment options. The alternate-day administration of crizotinib (200 mg, once daily) was started. The alternate-day treatment was continued but the dose was sequentially increased to 250 mg, twice daily. The alternate-day treat-

ment did not induce any signs of toxicity such as esophagitis or liver dysfunction. MRI showed the shrinkage of the spinal metastases two months after the initiation of the alternate-day administration of crizotinib (250 mg, twice daily) (Fig. 2B). Five months after the initiation of alternate-day administration, the regrowth of the spinal metastases was observed by MRI (Fig. 2C). The crizotinib dose was increased to 250 mg, twice daily. Fourteen days later, esophagitis re-developed and the treatment was stopped. EGD performed seven days after the discontinuation of crizotinib treatment, confirmed the improvement of esophagitis. It was difficult to treat this patient with cytotoxic agents due to her poor performance status. At the time, next generation ALK inhibitors were not yet commercially available. The alternate-day treatment of crizotinib (250 mg, twice daily) was expected to delay the progression of meningitis. The serum concentration of crizotinib reached 17.5 ng/mL at seven days after the re-initiation of treatment and 52.8 ng/mL after 29 days (Table). Crizotinib treatment was continued for 3 months without any adverse effects until the patient's neurological symptoms worsened.

Discussion

In phase I and II trials of crizotinib, three cases of esophagitis and one case of esophageal ulceration were reported among 255 patients (14). To our knowledge, there are six case reports of crizotinib-induced esophagitis (8-13). The mechanism of crizotinib-induced esophagitis is not clear. In our case, esophagitis was induced by administration of crizotinib at 250 mg, twice daily, but not by 200 mg, twice daily or the alternate-day administration at 250 mg, twice daily. The patient's serum concentration of crizotinib (468 ng/mL) at the first presentation of esophagitis was not higher than the serum concentrations observed in the clinical trials (15). The patient's esophagitis may have been related not only to the serum concentration of crizotinib, but also to other factors, including drug sensitivity. We decided to administer crizotinib on alternate days after the reduction of the daily dose failed due to toxicity. Thus far, there are no published data that support the alternate-day administration of crizotinib. However, the clinical benefit of the alternate-day administration of gefitinib, an EGFR-TKI, has been reported (16, 17). Satoh et al. suggested that the intermittent administration of gefitinib may be clinically equivalent to standard-dose gefitinib for cases of NSCLC with sensitive EGFR mutations in terms of progression free survival and overall survival (16). In our case, although the trough level of crizotinib was lower than the effective serum concentration, this dosing method was able to control disease progression for five months and improved the patient's performance status with manageable side effects. This alternate-day dosing method may be a therapeutic option when unmanageable toxicity is induced by crizotinib. More cases are needed to assess the efficacy of the alternate-day administration of crizotinib.

We reported a case of recurrent esophagitis induced by the administration of crizotinib (250 mg, twice daily). We could manage the side effects and control the progression of disease by the alternate-day administration of crizotinib.

Author's disclosure of potential Conflicts of Interest (COI).

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