Lung Cancer 88 (2015) 349–351

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Case report

Successful treatment with alectinib after crizotinib-induced esophageal ulceration

Yasuto Yoneshima[a], Isamu Okamoto[a,b,*], Tomotsugu Takano[a], Aimi Enokizu[a], Eiji Iwama[a,c], Taishi Harada[a], Koichi Takayama[a], Yoichi Nakanishi[a,b]

[a] Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[b] Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka, Japan
[c] Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

ARTICLE INFO

Article history:
Received 18 January 2015
Received in revised form 10 March 2015
Accepted 11 March 2015

Keywords:
Alectinib
Crizotinib
Esophageal ulceration
Anaplastic lymphoma kinase (ALK)
Non-small-cell lung cancer (NSCLC)

ABSTRACT

Crizotinib was the first clinically available inhibitor of the tyrosine kinase ALK, and next-generation ALK inhibitors, such as alectinib, are now under development. Although crizotinib is generally well tolerated, severe esophageal injury has been reported as a rare but serious adverse event of crizotinib therapy. We now describe the successful treatment with alectinib of a patient who developed crizotinib-induced esophageal ulceration.

1. Introduction

Crizotinib is a tyrosine kinase inhibitor for MET and ALK and has shown marked antitumor activity in patients with non-small cell lung cancer (NSCLC) positive for *ALK* rearrangement [1]. Although it is generally well tolerated, less than a third of patients treated with crizotinib develop significant adverse events (AE) that require dose interruption or reduction [2]. Severe esophageal injury has been reported as a rare but serious AE associated with crizotinib therapy [3,4].

Alectinib is a highly selective ALK inhibitor and was approved in 2014 for the treatment of *ALK* fusion gene-positive NSCLC in Japan. It has shown promising activity in patients with crizotinib-resistant disease and has been generally well tolerated in clinical trials [5]. The safety of alectinib for patients who develop crizotinib-induced esophageal ulceration has not been determined. We now describe the successful treatment with alectinib of a patient who developed crizotinib-induced esophageal ulceration.

2. Case report

A 52-year-old Japanese female never-smoker was diagnosed with stage IV (cT2aN2M1a) adenocarcinoma of the lung. The patient received 4 cycles of carboplatin and gemcitabine as a first-line chemotherapy followed by pemetrexed as a second-line. After 8 cycles of pemetrexed, the patient underwent palliative radiotherapy for superior vena cava syndrome. The patient subsequently showed evidence of progressive disease with bilateral pulmonary metastases and multiple bone metastases. After multiple regimens of chemotherapy, the primary tumor was found to harbor an *ALK* rearrangement by fluorescence in situ hybridization. The capsule form of crizotinib was administered orally at a dose of 250 mg twice daily. After 4 days of crizotinib treatment, the patient developed odynophagia and dysphagia. The patient had no condition such as rheumatological disease that predisposed her to have dysphagia. Although no esophageal abnormality was detected by computed tomography (CT) before crizotinib treatment (Fig. 1A), severe esophageal wall thickening was apparent after 4 days of treatment (Fig. 1B). Upper endoscopy showed circumferential ulcer with a white coating in the esophagus (Fig. 1C). Histopathologic examination of the ulcer edge revealed acute inflammatory changes. Crizotinib was discontinued, and the symptoms ameliorated within 1 week. Repeat endoscopy 10 days later showed no ulcer (Fig. 1D). Two months after crizotinib treatment, the patient showed evidence of progressive disease with growth of the lung

* Corresponding author at: Center for Clinical and Translational Research, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel.: +81 92 642 5378; fax: +81 92 642 5390.
E-mail address: okamotoi@kokyu.med.kyushu-u.ac.jp (I. Okamoto).

http://dx.doi.org/10.1016/j.lungcan.2015.03.012
0169-5002/

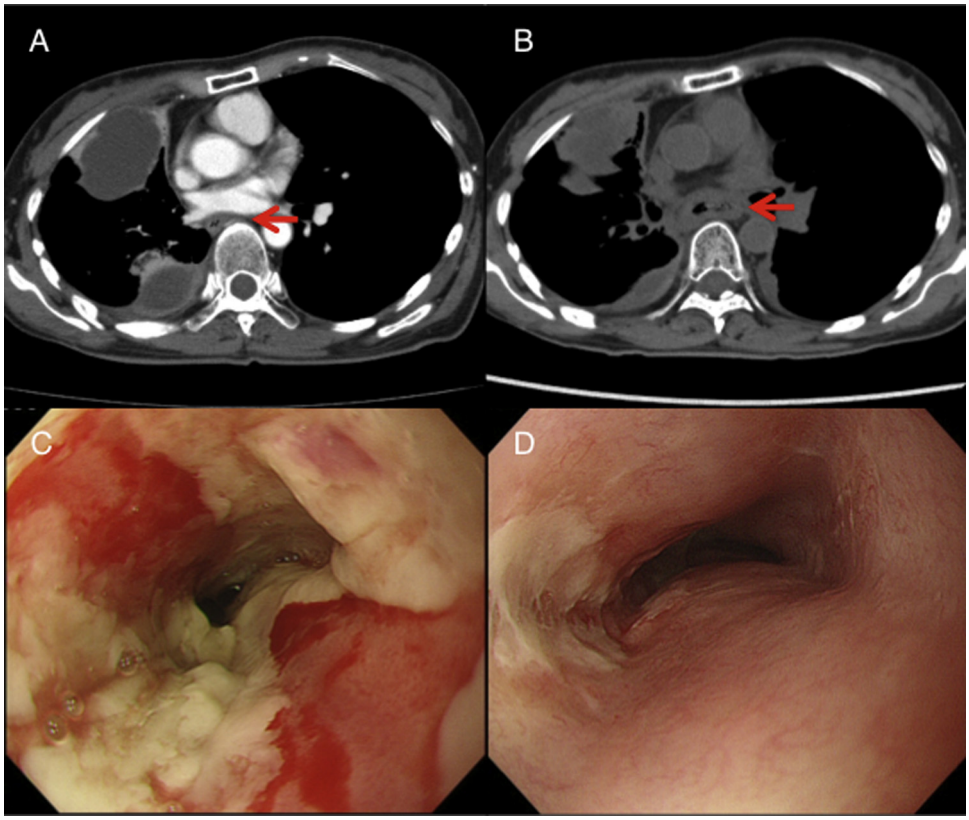

Fig. 1. CT and endoscopic imaging of esophageal ulceration. A CT scan showed no esophageal abnormality before crizotinib treatment (A) but severe circumferential esophageal wall thickening after 4 days of such treatment (B). Arrows indicate the esophagus. Endoscopy revealed circumferential ulcer of the esophagus after 4 days of crizotinib treatment (C) and disappearance of the ulcer at 10 days after cessation of the treatment (D).

tumors. After obtaining full informed consent regarding the risk of recurrent esophageal ulceration, we restarted the patient on crizotinib at an oral dose of 200 mg once daily ingested with a sufficient quantity of liquid in the sitting position and with co-administration of alginate sodium. After 7 days of crizotinib treatment, however, the patient manifested the same symptoms and upper endoscopy showed esophageal ulcer. Crizotinib was discontinued, and repeat endoscopy 10 days later revealed no ulcer. The clinical, endoscopic, and pathological findings were thus consistent with crizotinib-induced esophageal ulceration. The patient next received three regimens of chemotherapy, but she showed evidence of progressive disease with liver metastases. One year after crizotinib treatment, the patient was started on alectinib at an oral dose of 300 mg twice daily. Upper endoscopy showed no esophageal ulcer after 10 days of alectinib treatment. One month after the initiation of alectinib treatment, a CT scan revealed shrinkage of the tumors. The patient has remained on continuous alectinib treatment for 2 months with no evidence of esophageal ulcer.

3. Discussion

Crizotinib was the first clinically available ALK tyrosine kinase inhibitor for the treatment of *ALK* rearrangement-positive non-small cell lung cancer (NSCLC). Safety data from clinical trials indicate that crizotinib is well tolerated, with most adverse events (AEs) being of grade 1 or 2 [1,2,6]. Severe esophageal injury has been reported as a rare but serious AE associated with crizotinib therapy [3,4].

We here describe a case of crizotinib-induced severe esophageal ulceration that reappeared after discontinuation and resumption of crizotinib treatment. Adequate liquid intake in the standing position was previously found to prevent the recurrence of crizotinib-induced esophageal ulceration [4]. In the present case, however, the esophageal ulcer was recurrent with a sufficient quantity of liquid ingested in an adequate position and with co-administration of a mucosal protectant.

The biological mechanism of crizotinib-induced esophageal ulceration remains unclear. A previous study indicated that esophageal ulcer activates signaling by hepatocyte growth factor (HGF) and its receptor (MET) as a repair mechanism [7]. Given that crizotinib was originally developed as a MET inhibitor, blockade of HGF-MET signaling might contribute to the pathogenesis of crizotinib-induced esophageal ulceration. In contrast, alectinib is highly selective for ALK among various types of kinase enzyme [8]. The present patient received alectinib with no evidence of esophageal ulcer, suggesting that this AE is not the result of ALK inhibition but rather an off-target effect of crizotinib.

In conclusion, we successfully managed a patient who developed crizotinib-induced esophageal ulceration by full-dose treatment with alectinib. Alectinib is thus a potential effective and well-tolerated treatment option for patients for whom crizotinib has been discontinued because of severe esophageal injury.

Disclosure

The authors report that they have no relevant relationships to disclose.

Conflict of interest statement

None declared.

References

[1] Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693–703.

[2] Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011–9.

[3] Srivastava N, VanderLaan PA, Kelly CP, Costa DB. Esophagitis: a novel adverse event of crizotinib in a patient with ALK-positive non-small-cell lung cancer. J Thorac Oncol 2013;8:e23–4.

[4] Park J, Yoshida K, Kondo C, Shimizu J, Horio Y, Hijioka S, et al. Crizotinib-induced esophageal ulceration: a novel adverse event of crizotinib. Lung Cancer 2013;81:495–6.

[5] Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, et al. (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol 2013;14:590–8.

[6] Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.

[7] Baatar D, Jones MK, Pai R, Kawanaka H, Szabo IL, Moon WS, et al. Selective cyclooxygenase-2 blocker delays healing of esophageal ulcers in rats and inhibits ulceration-triggered c-Met/hepatocyte growth factor receptor induction and extracellular signal-regulated kinase 2 activation. Am J Pathol 2002;160:963–72.

[8] Sakamoto H, Tsukaguchi T, Hiroshima S, Kodama T, Kobayashi T, Fukami TA, et al. a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell 2011;19:679–90.