Afatinib-induced severe esophagitis in a lung cancer patient with an activated epidermal growth factor receptor mutation: A case report

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1. Introduction

Tyrosine kinase inhibitors (TKIs) for epidermal growth factor receptor (EGFR) are key drugs in non-small cell lung cancer (NSCLC) harboring activated EGFR mutations. Afatinib is a second-generation tyrosine kinase inhibitor that binds covalently to EGFR and inhibits it together with the inhibition of other Her family receptors (1). Recently, the role of afatinib has been closed up in 2 studies, a combined analysis of LuxLung 3 and 6 and LuxLung 7 (2, 3). The former study showed superiority of afatinib over the first-generation of EGFR-TKIs: only afatinib among EGFR-TKIs improved overall survival in comparison with platinum doublet. The superiority of afatinib was especially remarkable in NSCLC with exon 19 deletion (Ex19del). In LuxLung 7, afatinib was compared with gefitinib in a head to head randomized phase 2 study for NSCLC with activated EGFR mutations in the first line setting, and showed statistically significant improvement in progression-free survival (PFS). The major side effects of afatinib of grade 3 or more included diarrhea (12%), rash (9%), and stomatitis (4%) in LuxLung 7. Although mucosal toxicities are relatively popular in afatinib, severe esophagitis has not yet been reported associated with afatinib.

2. Case report

In April 2014, a 58-year-old, never-smoking Japanese woman had experienced recurrence of NSCLC following 15 months of disease-free interval after surgical resection and adjuvant chemo-therapy for pT1aN0M0 adenocarcinoma of the lung. Because her NSCLC carried EGFR Ex19del, gefitinib had been started. Nine months later, brain metastasis developed. Thereafter, she underwent erlotinib monotherapy, pemetrexed combined with bevacizumab, and then erlotinib combined with bevacizumab. In February 2016, carcinomatous meningitis was diagnosed, and 40 mg afatinib once a day was applied for it. Although paronychia and diarrhea developed, 40 mg afatinib could be continued. On the 37th-day of afatinib treatment, she admitted emergently because of disturbance of consciousness and poor appetite probably due to progression of meningitis. Her clinical course after the start of afatinib was shown in Fig. 1. Food intake was remarkably decreased by nausea and vomiting, but oral medication had been continued without changing the doses. On the 39th day of afatinib treatment, she complaint odynophagia by sour food. Endoscopic examination on the next day revealed the presence of erosive esophagitis extending throughout the entire esophagus (Fig. 2A). In contrast, gastric mucosa appeared to be almost intact (Fig. 2B), indicating that the pathological process was strictly limited to the esophagus. Vascular dilations and neovascularization were observed by the narrow band imaging (Fig. 2C). Biopsy of the esophageal mucosa revealed severe chronic inflammation with neutrophilic infiltration (Fig. 2D). Drug-induced esophagitis due to afatinib is most likely, although complete elimination of the contribution of the other drugs to it is difficult. Afatinib was discontinued. Endoscopic examination to observe the response of the esophagitis to...
discontinuation of afatinib was not performed due to her poor general condition. Afatinib was not reintroduced because of tumor progression.

3. Discussion

It is sometimes difficult to determine the causative drug of an observed side effect, when multiple drugs are being administered. When the patient complained of abnormal sensation on swallowing, she was taking loxoprofen (180 mg/day), pregabalin (150 mg/day), lorazepam (1.5 mg/day), a formulation of butyric acid bacteria, and amino acid supplements together with afatinib. However, all drugs and supplements including afatinib were started more than 1 month before developing the esophagitis. The latent period seemed to be too long, if one of these drugs and supplements caused her esophagitis. Some event should have triggered the development of esophagitis.

Her appetite was very poor for several days before developing the esophagitis. It is well known that blood concentration of a drug is affected by food intake. One possible cause of her esophagitis is an increased blood concentration of a drug to the toxic level by taking it on persistent empty stomach. Whereas increase of serum concentration due to empty stomach is not reported neither with loxoprofen, pregabalin, nor lorazepam, that of afatinib is reported to increase to almost twice when it was taken on empty stomach compared with administration on full stomach. In addition, the doses of loxoprofen, pregabalin and lorazepam appear to have had a sufficient safety margin in her actual usage. These results suggest that the probable causative drug is considered to be afatinib. Although afatinib had been taken in empty stomach throughout the treatment, prolonged starved condition might have further increased serum concentration of afatinib resulting in the development of the severe esophagitis. Increased severity of the other toxicity of afatinib such as rash and paronychia during the time period with poor appetite may support this speculation.

Esophagitis induced by molecular-targeted drugs is rare: There is no report of the esophagitis induced by EGFR-TKIs, whereas there are 5 reports of esophagitis induced by crizotinib, an inhibitor of anaplastic lymphoma kinase (4-8). The first and second generations of EGFR-TKIs showed distinct inhibitory activity for wild type EGFR, although less effective than for activated EGFRs. EGFR is expressed mucosal surface of the alimentary tract, and its inhibition by EGFR-TKIs can be a cause of mucosal damage. Neither gefitinib nor erlotinib had induced esophagitis in our patient. In contrast, severe esophagitis developed during the treatment with afatinib only when the appetite of the patient was decreased remarkably. To our knowledge, this is the first report of afatinib-induced and also EGFR-TKI-induced esophagitis.