CASE REPORT

Gefitinib for Non-Small Cell Lung Cancer Patients with Liver Cirrhosis

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Abstract

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), such as gefitinib or erlotinib, is mainly metabolized in liver. To date, the safety data on administrating EGFR-TKI to patients with liver dysfunction is quite limited. Here, we administered gefitinib to two adenocarcinoma patients with liver cirrhosis, and one patient with EGFR gene mutation in exon 21 achieved long stable disease (SD) without any toxicity. Pharmacokinetic data of alternate days administration in these patients were similar to those of daily administration in patients with normal liver function. Although further studies are needed, a reduced dose of gefitinib might be feasible for patients with liver dysfunction.

Key words: gefitinib, liver cirrhosis

(Inter Med 48: 1677-1679, 2009)  
(DOI: 10.2169/internalmedicine.48.2401)

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), such as gefitinib or erlotinib, is mainly metabolized in the liver. To date, the safety data on administering EGFR-TKI to patients with liver dysfunction is quite limited. Here, we administered gefitinib to two patients with adenocarcinoma of the lung with liver cirrhosis, and analyzed pharmacokinetics (PK).

Case Report

Case 1

A 57-year-old woman with liver cirrhosis due to idiopathic portal hypertension developed two pulmonary nodules, one in the left upper lobe and the other in the right lower lobe, and sputum cytology revealed adenocarcinoma. Under the diagnosis of double primary lung cancer (cT1N0M0, stage IA), stereotactic radiosurgery (48 Gy) was performed on each nodule. Three months later she developed radiation pneumonitis and was treated with steroids and then home oxygen therapy. During the subsequent four months her right lower lobe nodule gradually increased in size. Her recurrent tumor had caused obstructive pneumonia; however, no distant metastases or lymph node metastases were demonstrated. Her Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 3. She had ascites, hyperbilirubinemia (1.8 mg/dL), and hypoalbuminemia (2.8 g/dL); her Child-Pugh class was B. She had undergone endoscopic clipping therapy for esophageal varices 10 years previously. Neither surgical resection nor conventional cytotoxic chemotherapy was applicable due to her hepatic and respiratory impairment and poor PS. We recommended that she receive the best supportive care; however, she was strongly in favor of anti-cancer treatment. Epidermal growth factor receptor (EGFR) mutation status, examined by the direct sequence method, revealed that she had no EGFR mutations in exons 19 to 21. She had favorable clinical factors in predicting the efficacy of gefitinib, such as woman sex, adenocarcinoma histology, a never-smoker, and Asian ethnicity. Therefore, we administered gefitinib, monitoring the blood concentration after careful discussion and obtaining informed consent. We initially administered gefitinib on alternate days for two weeks based on the previous phase I study, which had revealed that an average blood level of gefitinib is higher in patients with hepatic impairment than in those with normal liver function (1). After confirming the safety of alternate-day administration, we administered gefitinib...
gefitinib daily for two weeks and then continued on alternate days. Computed tomography (CT) scan of the chest confirmed stable disease (SD) with remarkable decrease of the serum level of carcinoembryonic antigen (CEA). No apparent toxicity, hematologic or non-hematologic, was observed during the initial month. She was therefore discharged and referred to her local hospital; however, three months after beginning treatment she presented with ruptured esophageal varices. In spite of intensive treatment her liver function gradually deteriorated, and she died on day 106 from the beginning of gefitinib administration.

Case 2

A 62-year-old woman with liver cirrhosis due to hepatitis C virus infection presented with headache and back pain. CT of the chest confirmed a 2.8 cm nodule in the right lung, and magnetic resonance imaging (MRI) of the brain revealed multiple brain tumors. Histopathologic study of transbronchial biopsy specimens revealed adenocarcinoma. She was in a good general condition (PS 1), had fair liver function (Child-Pugh class A), and reduced platelet count (5.1×10⁴/μL). Conventional cytotoxic chemotherapy was not feasible for her due to thrombocytopenia, however, sequencing analysis of EGFR by direct sequence method using her biopsy specimens revealed a point mutation of exon 21 (L858R). Therefore, we started administration of gefitinib on alternate days while monitoring blood concentration after obtaining informed consent. She achieved long stable disease (SD), and has remained progression-free for at least 8 months without toxicity. No hematologic or non-hematologic toxicities were observed.

### Pharmacokinetic Analysis

Table 1 shows the pharmacokinetic (PK) data of gefitinib in these two patients. Blood concentration of gefitinib was determined by high-performance liquid chromatography with tandem mass spectrometry detection at Shinnihon-kagaku Co., Ltd. (Wakayama, Japan). When administered alternatively, AUC₀-₂₄ was 4,761.2 ng/mL in case 1 and 3,861.1 ng/mL in case 2, respectively.

### Discussion

In gefitinib metabolism, the liver plays the principal role and gefitinib excretion in the urine is reportedly less than 4%. In order to investigate the safety and tolerability of gefitinib in patients with hepatic impairment, a phase I study was carried out. In the study, 250 mg single-dose gefitinib was administered to non-cancer patients with mild, moderate or severe hepatic impairment due to cirrhosis and an average 3.1-fold increase in area under the curve (AUC) of gefitinib was observed in patients with moderate or severe hepatic impairment compared to those with normal hepatic function (1). As anticipated, the blood concentration was higher when gefitinib was administered daily than on alternate days. In addition, when administered on alternate days, PK data were similar in the two patients. In the Japanese phase I study of gefitinib, six patients, including non-small cell lung cancer, colorectal cancer, and head and neck cancer with normal liver function, were given 225 mg gefitinib daily (2). When the dose was adjusted to 250 mg daily, the mean area under the curve (AUCₜ₋₂₄) was 6,530±3,370 ng/mL (data provided by AstraZeneca). In the present cases when administered alternatively, AUC₀-₂₄ was 4,761.2 ng/mL in case 1 and 3,861.1 ng/mL in case 2. Although inter-subject variability of AUC exists, a reduced dose of gefitinib might be safe and sufficient in patients with impaired hepatic function. The AUC₀-₂₄ of case 2 may seem slightly low, and if she had been administered a greater dose of gefitinib, she might have achieved partial or complete response. However, she refused dose escalation for fear of adverse toxicity.

In September 2008, the Food and Drug Administration (FDA), OSI and Genentech issued a warning that patients with hepatic impairment should be monitored closely during therapy with erlotinib and dosing should be interrupted or discontinued if changes in liver function are severe, based on cases of liver failure and hepatorenal syndrome, including fatalities reported during its use, particularly in patients with baseline hepatic impairment (3). In our experience, case 1 died of ruptured esophageal varices. Although it is difficult to evaluate, it is possible that gefitinib contributed to her early mortality.

Currently, it is widely accepted that a significantly high proportion of patients with EGFR gene mutation respond to EGFR-TKI (4). In addition, the results of the IRESSA Pan-Asian Study (IPASS) suggest that even first-line treatment with gefitinib might be recommended for patients with EGFR gene mutation (5). It is therefore critical to determine whether to treat and how to treat patients with liver dysfunction especially when their tumors harbor EGFR gene mutation. Further studies are needed to investigate a safe and effective way of administering EGFR-TKI to patients with liver dysfunction.
1. Pharmacokinetic data of single dose IRESSA 250 mg in patients with hepatic impairment due to cirrhosis without cancer. In-house data of AstraZeneca (Osaka, Japan), October 2006.