Successful Treatment of Non-small Cell Lung Cancer with Gefitinib after Severe Erlotinib-related Hepatotoxicity

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Abstract

Gefitinib and erlotinib are first-generation small molecular inhibitors of EGFR tyrosine kinase activity. To the best of our knowledge, to date, two reports have stated that patients with NSCLC who develop severe hepatotoxicity secondary to gefitinib treatment can be safely switched to erlotinib. However, the reverse situation has not been reported. Here, we present the first case with non-small cell lung cancer harboring EGFR mutation who developed grade 3/4 hepatotoxicity after initiation of erlotinib, which resolved when therapy was changed to gefitinib. As far as we know, this is the first report showing the efficacy of gefitinib for a non-small cell lung cancer patient who developed severe hepatotoxicity while under erlotinib therapy.

Key words: non-small cell lung, gefitinib, erlotinib, hepatotoxicity

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Introduction

Common toxicities of first-generation small molecular inhibitors of EGFR tyrosine kinase activity, gefitinib and erlotinib include skin rash, diarrhea and mucositis (1, 2). Compared to these toxicities, hepatotoxicity is relatively under-appreciated. To the best of our knowledge, two reports have stated that patients with NSCLC who develop severe hepatotoxicity secondary to gefitinib treatment can be safely switched to erlotinib (3, 4). However, the reverse situation has not been reported as far as we can discern. Here, we present a patient who developed severe hepatotoxicity while receiving erlotinib treatment, but could be safely switched to gefitinib therapy.

Case Report

A 64-year-old woman who had never smoked was referred to our hospital for back pain and dyspnea. A chest X-ray showed left pleural effusion and multiple small nodules scattered on bilateral lung fields (Fig. 1). A computed tomography (CT) scan of the chest revealed disseminated nodules on the left pleura and multiple pulmonary nodules scattered throughout the bilateral lungs and bone scintigraphy showed multiple bone metastases (Fig. 2A, B). Contrast-enhanced brain magnetic resonance imaging showed multiple brain metastases (Fig. 2C). She had no symptoms of brain metastases. A cytological examination of the pleural effusion revealed adenocarcinoma. Her disease was diagnosed as adenocarcinoma of the lung with multiple metastases (cT4N3M1 UICC 6th). Mutation analysis with the PNA-LNA clamp method (1) of samples obtained from the left malignant pleural effusion revealed a deletion of exon 19 in the epidermal growth factor receptor (EGFR) gene.

Erlotinib was administered orally at a dose of 150 mg daily as an initial therapy, because erlotinib is highly effective for patients with adenocarcinoma of the lung harboring activating EGFR mutations. Five weeks after the start of treatment (day 35), a CT scan revealed obvious tumor shrinkage as well as disappearance of the pleural effusion and the multiple brain metastases. Laboratory findings simultaneously indicated a substantial increase in serum transaminase levels (AST, 190 U/L; normal range, <40 U/L; ALT, 129 U/L; normal range, <35 U/L; Fig. 3). The total bilirubin (TBL) level was within the normal limit, and the serum alkaline phosphatase (ALP) level was 819 U/L, which was probably derived from multiple bone metastases be-
cause the ALP level at the first visit was 1,614 U/L. Erlotinib was discontinued and ursodeoxycholic acid was started. The AST and ALT levels reached 592 U/L and 617 U/L respectively at the peak on day 39. These adverse events were assessed as grade 3 transaminase elevation based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 4.0). After improvement of transaminase levels to grade 1 on day 46, we recommenced treatment with 100 mg/day of erlotinib. The AST and ALT levels began to increase once again, reaching 891 U/L and 427 U/L after only 3 days of readministration and 1,008 U/L and 518 U/L respectively, on the following day (Fig. 3). The toxicity was so severe that we were forced to discontinue the erlotinib treatment. After amelioration of transaminase levels on day 61, we initiated treatment with another EGFR-TKI, gefitinib at a dose of 250 mg once daily accompanied by careful monitoring because her lung cancer progressed slightly. She has been continuing gefitinib for 36 weeks with no evidence of increased transaminase levels or disease progression.

**Discussion**

Gefitinib and erlotinib are first-generation small molecular inhibitors of EGFR tyrosine kinase activity; they play a key role in the treatment of advanced non-small cell lung cancer (NSCLC). This has led to a paradigm shift in the treatment of patients with advanced NSCLC (1, 2). The common toxicities of gefitinib and erlotinib include skin rash and diarrhea. Although the incidence of hepatotoxicity is thought to be lower than that of these adverse effects, some case reports have also noted that erlotinib can cause fatal fulminant hepatitis in patients with NSCLC (5, 6).

The present case had multiple brain metastases, but she had no symptoms of brain metastases. The primary treatment for brain metastases in patients with lung cancer has traditionally consisted of whole-brain radiotherapy, surgery, or radiosurgery, whereas systemic chemotherapy has been thought to play a limited role because of the belief that the brain is a pharmacologic sanctuary site (7, 8). However, several studies have documented the effectiveness EGFR-TKI in the treatment of brain metastases of lung cancer harboring EGFR mutations. Katayama et al (9) reported the effectiveness of erlotinib for the treatment of brain metastases after gefitinib failure. Togashi et al (10) reported the possibility that erlotinib treatment could be more effective for brain...
metastases than gefitinib treatment due to its higher penetration rate to cerebrospinal fluid. For these reasons, we chose erlotinib treatment for the present case with advanced lung adenocarcinoma harboring EGFR mutation (a deletion of exon 19) involving multiple brain metastases.

Several patterns of drug-related hepatotoxicity are recognized, each with a different mechanism of injury. They are distinguished into hepatocellular or cytolytic injury, cholestatic injury, hypersensitivity or immunologic injury and mitochondrial injury by means of biochemical, clinical, histologic characteristics and chronologic features (11). The present case did not consume alcohol, had no previous renal or liver diseases and had not taken any other medications or supplements. Markers for current viral hepatitis A, B, C were negative. An abdominal CT scan revealed normal liver parenchyma and the absence of liver metastases and biliary obstruction. A drug lymphocyte stimulation test (DLST) for erlotinib was negative and she had no systemic features such as fever, rash, and eosinophilia, therefore hypersensitivity or immunologic hepatotoxicity were considered to be unrelated to the hepatotoxicity. The marked elevations of AST and ALT without changes of TBL and ALP suggested hepatocellular injury. Unfortunately we could not perform biopsy of the liver and it was impossible to investigate the nature of liver injury any further.

Two reports have stated that patients with NSCLC who develop severe hepatotoxicity secondary to gefitinib treatment can be safely switched to erlotinib (3, 4). However, the reverse situation has not been reported as far as we can discern. Erlotinib and gefitinib share a common chemical backbone structure and exhibit similar disposition characteristics in humans after oral administration. Although both are metabolized primarily by the cytochrome P450 (CYP) 3A4 with >80% of the administered dose being excreted into the feces (12), they have such differential metabolizing enzyme profiles that gefitinib is more susceptible to CYP3As and CYP1A1-mediated metabolism than erlotinib and that CYP1 A2 is associated with the metabolism of erlotinib but not gefitinib (13). This difference is partly because they differ in the substituents attached to the quinazoline and aniline rings and in the inactive ingredients listed on the label information released by pharmaceutical manufacturers. These minor alterations in the metabolism profiles might account for the different hepatotoxic effects. As far as concomitant drugs, the patient did not receive any medications that could influence the pharmacokinetics of gefitinib or erlotinib.

We suggested the possibility that gefitinib is an effective and well-tolerated treatment option for patients who develop severe hepatotoxicity while under erlotinib therapy.

The authors state that they have no Conflict of Interest (COI).

References


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