Recurrent Gefitinib-induced Interstitial Lung Disease

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Abstract

Gefitinib, the epidermal growth factor receptor tyrosine kinase inhibitor, is effective for patients with non-small cell lung cancer. However, a serious adverse effect, interstitial lung disease (ILD), has been reported. The re-administration of gefitinib might be considered when there is no other choice of treatment and a therapeutic effect can be expected; however, there is no published data on the safety of restarting gefitinib after its discontinuation in cases suspected of having gefitinib-induced ILD. We report a case with recurrent gefitinib-induced ILD, which suggests that re-administration of gefitinib should be considered cautiously in patients who have previously developed gefitinib-induced ILD.

Key words: non-small cell lung cancer, drug-induced lung injury, gefitinib, epidermal growth factor tyrosine kinase


Introduction

Gefitinib is an oral selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase; it is effective for the treatment of patients with advanced non-small cell lung cancer (NSCLC). The response rate with gefitinib (250 mg per day) in two randomized double-blind phase II trials of NSCLC patients who failed to respond to platinum-based chemotherapy (IDEAL-1 and IDEAL-2) was 18.4% and 11.8%, respectively (1, 2). In the IDEAL-1 study, a higher response rate in Japanese patients compared to non-Japanese patients (28% vs. 10%) was reported. In these studies, disease-related symptoms were also found to be improved with gefitinib monotherapy. Gefitinib is regarded as a relatively safe agent, although toxic effects such as diarrhea and skin rash have been reported (1, 2). In Japan, gefitinib was approved in July 2002 for the treatment of inoperable or recurrent NSCLC. However, shortly after gefitinib was approved, pulmonary toxicity, including interstitial lung disease (ILD), was reported as a serious, occasionally fatal, adverse effect (3-5). On the other hand, one may wish to consider, or patients may request, re-administration of gefitinib when there has been a previous response but suspected gefitinib-induced ILD developed, particularly in cases in which that there is no other choice of treatment. To date, no information on the safety of restarting gefitinib after its discontinuation in suspected cases of ILD has been published. We report the case of a patient who developed recurrent gefitinib-induced ILD.

Case Report

A 59-year-old man was admitted to our hospital due to an abnormal shadow in the anterior mediastinum on chest computed tomography (CT). He had been diagnosed as having thrombocytopenia 6 years before admission, and had smoked 1.5 packs of cigarettes daily from the age of 20 years until admission. His performance status was 1. On pathology, the surgical biopsy of the mediastinal tumor showed a poorly differentiated adenocarcinoma positive for thyroid transcription factor-1 (TTF-1), which indicated that it was a lung metastasis. Although the primary lesion could not be determined, abdominal para-aortic lymph node metastases were also found, and the patient was diagnosed as having stage IV lung adenocarcinoma. No EGFR gene mutation was detected in the mediastinal tumor tissue. The patient received one cycle of chemotherapy with carboplatin and paclitaxel as first-line therapy. The size of the tumor did not change after treatment. However, the patient developed petechiae on the chest wall and limbs; the patient had a grade 3 thrombocytopenia 41 days after the administration of car-

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boplatin and paclitaxel. Therefore, the patient was given gefitinib (250 mg per day) as second-line therapy. Before the start of gefitinib, no preexisting interstitial shadow on chest high-resolution CT was confirmed. After taking gefitinib, the patient’s pleural effusion decreased, and his tumor marker levels improved (carcinoembryonic antigen (CEA): from 56.4 ng/ml to 35.6 ng/ml) (Fig. 1).

However, after 23 days of gefitinib therapy, the patient developed a high fever and shortness of breath, and he was admitted to hospital 2 days later. The arterial blood gas analysis revealed hypoxia (PaO₂: 46.9 Torr on room air). His serum surfactant protein (SP)-A level was elevated (from 24.0 ng/ml to 52.8 ng/ml) on the day of admission, whereas the SP-D and KL-6 levels were not increased (Fig. 1). Chest thin-slice CT showed a new ground-glass shadow in the left lower lobe (Fig. 2). Bronchoalveolar lavage (BAL) of the left lower lobe (B⁹) was performed. The total cell count could not be assessed due to the low recovery rate (7%). Nevertheless, the differential fraction of lymphocytes was increased (23%), and no neutrophils or eosinophils were detected in the BAL fluid. No malignant cells and no pulmonary pathogens, including bacteria, fungi, and Pneumocystis, were present in the BAL fluid. Although the peripheral blood lymphocyte stimulating test (DLST) with gefitinib was negative, ILD associated with gefitinib was suspected. Gefitinib was stopped, and intravenous high-dose methylprednisolone (1,000 mg daily for 3 days) treatment was started on the same day. The patient’s symptoms and radiological findings improved immediately. The steroid dose was tapered and then stopped 2 months later.

During follow-up, the patient received no further anticancer treatment. However, his left malignant pleural effusion...
became enlarged and his general fatigue worsened, so that the patient wished to have another course of anti-cancer therapy. Due to the presence of thrombocytopenia, chemotherapies that had hematotoxicity were considered to be too risky. Although ILD had appeared during the last gefitinib treatment, gefitinib treatment had been effective with respect to decreasing the pleural effusion and the tumor marker level. Since the patient and his family wished to restart gefitinib and fully understood the risk of recurrent ILD, we decided to re-administer gefitinib. The patient was admitted and was given oral gefitinib for 7 days followed by 2 weeks rest, which was defined as 1 cycle. After restarting gefitinib, the patient’s disease stabilized; both the CEA value and the tumor size remained stable. However, hypoxia (PaO₂ 54.6 Torr on room air) and high fever appeared on day 5 of the third course. Thin-slice CT revealed multiple ground-glass shadows not only in the left lower lobe but also in the other lobes (Fig. 3). The patient’s serum SP-A, SP-D, and KL-6 levels were not elevated at that time (Fig. 1). Although BAL was not repeated with this episode, the lung infiltration was diagnosed to be definite recurrent gefitinib-induced ILD, since the ILD was recurrent with re-administration of gefitinib. Therefore, gefitinib was discontinued, and his symptoms and radiological findings immediately improved after intravenous, high-dose methylprednisolone treatment. Subsequently, the steroid dose was tapered and then stopped 2 months later. The patient was then discharged to a hospice where he received supportive care.

Discussion

The incidence of gefitinib-related ILD in Japan has been reported to be 4.0%, and in 31.6% of these cases it was fatal (6). Despite this serious adverse effect, gefitinib has low hematologic toxicity. Therefore, gefitinib appears to be the optimal choice for NSCLC patients in whom no other chemotherapies can be used due to their hematologic toxicity. To date, however, there have been no reports dealing with the safety of re-administering gefitinib to patients who have had suspected gefitinib-induced ILD.

In general, drug re-challenge is contraindicated in patients who have experienced acute drug-induced ILD. Nevertheless, it has been shown that re-challenge might be considered under the following conditions (7): (i) there remains a doubt regarding the role of the drug, (ii) the drug is essential to the management of the patient, (iii) no other drug can be used due to their hematologic toxicity, and (iv) no reported adverse effects following rechallenge with the drug are known. Indeed in the present case, no other anti-tumor drug could be used due to the presence of thrombocytopenia, and the initial gefitinib

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**Figure 3.** Thin-slice CT findings before (A) and after (B) the second ILD episode. New ground-glass shadows are seen not only in the left lower lobe but also in the other lobes (B). The left malignant pleural effusion was not seen before the second ILD because the pleural fluid was drained therapeutically just before the third course of gefitinib (A).
treatment was associated with an apparent anti-tumor response. Moreover, no information about the adverse effects of gefitinib re-challenge was available at that time. Therefore, we decided to re-administer gefitinib under strict medical supervision. Although a resting period of 2 weeks was instituted after a 7-day course of gefitinib, ILD recurred during the third course of treatment with gefitinib. It is worth noting that the ILD recurrence was more severe than the first occurrence. Furthermore, both episodes of ILD responded completely to corticosteroid therapy. These findings indicate that, in the present case, immunological activation rather than direct drug cytotoxicity might be involved in the pathogenesis of gefitinib-induced ILD. However, more cases who have had gefitinib-induced ILD and received gefitinib re-administration need further analysis in order to determine the risk and features of recurrent ILD, and to elucidate the precise mechanism of gefitinib-induced ILD.

It has been reported that serum ILD markers, especially SP-A and SP-D, increase at the onset of gefitinib-induced ILD (8, 9). In the present case, although the SP-A was elevated at the onset of the first ILD episode, it did not increase at the onset of the second ILD episode. Moreover, the SP-D and KL-6 levels did not appear to reflect the onset and clinical course of ILD. This discrepancy may be due to the fact that this patient’s SP-D and KL-6 levels were already high prior to gefitinib treatment, suggesting that they were produced by cancer cells. This indicates that serum ILD markers, which are routinely measured for diagnosing other types of ILD in Japan, do not always reflect the clinical status of gefitinib-induced ILD.

In conclusion, we have reported a case of recurrent gefitinib-induced ILD. Re-administration of gefitinib should be considered cautiously in patients who have developed ILD following its use, even if a therapeutic effect could be anticipated.

References