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CASE STUDY

Acute lung injury as a possible adverse drug reaction related to gefitinib

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Acute lung injury as a possible adverse drug reaction related to gefitinib. R. Ieki, E. Saitoh, M. Shibuya. ©ERS Journals Ltd 2003.

ABSTRACT: Gefitinib is a potent drug used in the treatment of nonsmall-cell lung cancer (NSCLC).

Gefitinib acts by inhibition of the epidermal growth factor receptor tyrosine kinase. Clinical trials have confirmed the efficacy of gefitinib for NSCLC. Adverse drug reactions, although frequent, are mild, and include acne-like skin rash and diarrhoea.

The present study describes the case of a 56-yr-old male with NSCLC who, 4 weeks after treatment with gefitinib, suffered from a severe alveolar haemorrhage diagnosed by bronchoalveolar lavage.

This is the first case report of an acute life-threatening lung injury in a patient with nonsmall-cell lung cancer who had been given gefitinib.

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In recent years, several molecular targets relevant to cancer cell growth have been identified, and consequently, different selective inhibitors have been developed. The tyrosine kinase growth factor receptors, such as epidermal growth factor receptor (EGFR), and the protein kinases play an important and complex role in neoplastic growth, apoptosis and angiogenesis. The EGFR is expressed in a majority of nonsmall-cell lung cancers (NSCLC). In several studies, EGFR has been associated with a poor prognosis in lung cancer patients. Gefitinib (ZD1839 (Iressa); Astrazeneca, Osaka, Japan) is an orally active agent, which acts by inhibition of the EGFR tyrosine kinase, reversibly inhibiting critical downstream signalling and resulting in cancer cell growth arrest [1, 2]. Gefitinib has been demonstrated to have antitumour activity against a variety of human cancer cell lines expressing EGFR, including NSCLC, ovarian, breast and colon cancers [3]. It has been reported that gefitinib is well tolerated, with frequent, but mild, adverse drug reactions. Reported complications include acne-like skin rash, diarrhoea, nausea, vomiting and asthenia [4]. This case report describes a patient who had been given gefitinib and developed a severe alveolar haemorrhage.

Case history

A 56-yr-old male was admitted to hospital with a right cervical lymph node swelling and an abnormality on chest radiograph that was discovered in December 2000. The patient had a history of 20 pack-yrs of cigarette smoking and had gout. He was diagnosed with lung cancer (adenocarcinoma) by a transbronchial biopsy. The patient′s clinical stage was tumour (T)2, node (N)3, metastasis (M)1, with multiple pulmonary metastases. He experienced a partial response after treatment with two combined chemotherapy regimens (a course of cis-diaminedichloroplatinum (CDDP) and irinotecan, three courses of CDDP and gemcitabine). Five months later, his pulmonary disease and symptom recurred. However, he did not respond to two courses of combined chemotherapy consisting of CDDP and docetaxel that he received at the time.

Therefore, the patient was given gefitinib at the 250 mg dose level. Concomitant use of other drugs was not permitted. Although he did not experience an objective response, he had a decrease in pain from pleural metastases following gefitinib treatment.

However, 4 weeks after gefitinib treatment, he presented a 5-day history of progressive exertional dyspnoea and a cough with haemoptysis. His vital signs included a temperature of 37.5°C, a blood pressure of 110/70 mmHg, a pulse of 114 beats·min^{-1} and a respiratory rate of 30 breaths·min^{-1}. There was no jugular venous distention. Chest examination revealed left basilar inspiratory crepitations. Cardiac auscultation was normal. There were no signs of oedema, petechiae or subcutaneous bleeding. The chest radiograph done at that time revealed extensive bilateral interstitial infiltrates (fig. 1). The chest computed tomography scan demonstrated bilateral ground-glass attenuation and right lung cancer with multiple pulmonary metastases (fig. 2). Arterial blood gas analysis performed while the patient was breathing room air showed a pH of 7.46, arterial oxygen tension of 6.4 kPa, arterial carbon dioxide tension of 4.4 kPa and an arterial oxygen saturation measured by pulse oximetry (Sp,O_2) of 85%. A complete blood count showed white blood cells 10,100 mm^3, haemoglobin 10.8 g·dL^{-1} and C-reactive protein 8.9 mg·dL^{-1}. He had no circulating antineutrophil cytoplasmic antibodies and no antiglomerular basement membrane antibodies. Renal and liver function tests were within normal limits, including a lactate dehydrogenase level of 205 IU·L^{-1}. Electrocardiography showed sinus tachycardia.

Gefitinib treatment was withdrawn and empirical treatment with intravenous minomycin and meropenem was started. Supplemental oxygen was given by nasal cannula at 4 L·min^{-1}.

Fibreoptic bronchoscopy with bronchoalveolar lavage (BAL)

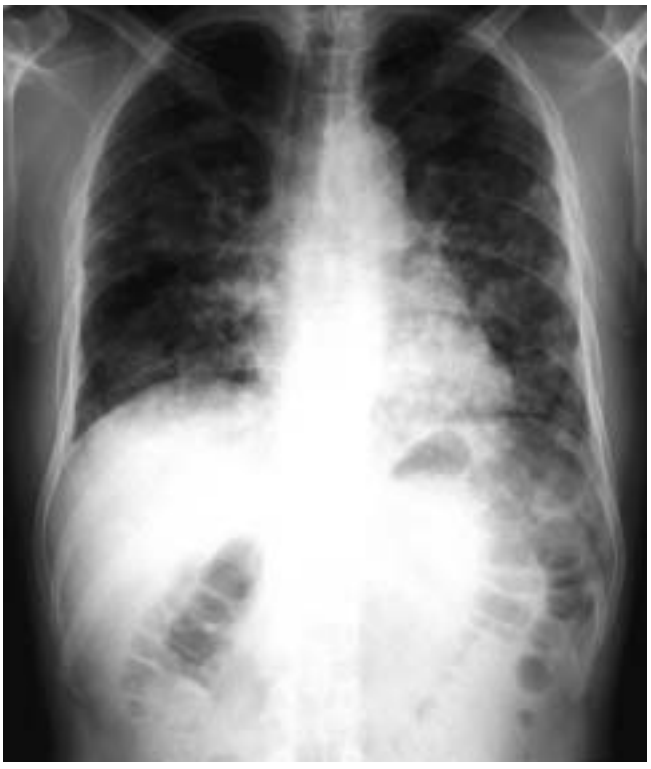

Fig. 1. – Chest radiograph showing extensive bilateral interstitial infiltrates after 4-weeks gefitinib treatment.

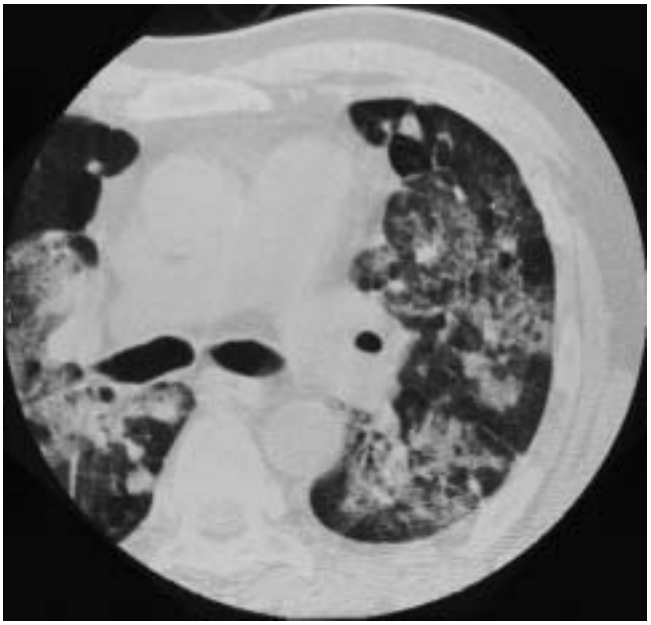

Fig. 2. – Chest computed tomography scan demonstrating bilateral ground-glass attenuation and right lung cancer with multiple pulmonary metastases.

was performed and revealed no evidence of *Pneumocystis carinii* pneumonia (PCP), acid-fast bacilli, fungi or malignancy, except for alveolar haemorrhage. The BAL analysis showed haemosiderin-laden macrophages and an abnormal leukocyte count (90% lymphocyte, 10% neutrophil).

The patient clinical state deteriorated and a high dose of methylprednisolone and carbazochrome sodium sulphonate were added to deal with the alveolar haemorrhage. He was supported by full-face mask ventilation and a repeated addition of high-dose methylprednisolone. By day 28 after admission, the patient′s respiratory status was gradually improved with an S_{p,O_2} of 98% by nasal cannula at 4 $L \cdot min^{-1}$. Special stains and subsequent cultures were negative for fungal, mycobacterial, viral and other organisms.

Although the patient′s lung cancer was gradually increased, his respiratory function continued to improve. At the time, the patient was discharged home, 2 months after admission; he was on oral prednisone 25 $mg \cdot day^{-1}$ and had an S_{p,O_2} of 95% while breathing ambient room air.

Discussion

The EGFR belongs to a subfamily of four closely related receptors: EGFR, Her2/neu, Her3 and Her4. The EGFR is expressed, overexpressed or dysregulated in many human solid tumours. The EGFR is expressed in a majority of NSCLCs. In several studies the EGFR of lung cancer patients has been associated with a poor prognosis. Recent findings have elucidated the role that the EGFR plays in tumour vascularisation. The development of new vasculature is vital in supporting tumour growth. Tumour invasiveness and metastasis are positively correlated with positive EGFR status in lung carcinomas. Thus, the EGFR represents a logical target for novel agents that can interrupt this mitogenic pathway and therefore interfere with cancer growth [5]. Given the importance of EGFR, EGFR-targeted cancer therapies are currently being developed. A recent highlight has been the development of quinazoline-derived agents that are specific adenosine triphosphate competitors of EGFR tyrosine kinase. Gefitinib is a representative of this type of agent. Gefitinib acts by inhibiting the EGFR tyrosine kinase, reversibly inhibiting critical downstream signalling, resulting in cancer cell growth arrest.

According to the results of a phase-trial, the most frequently reported adverse events included skin rash, diarrhoea, nausea, vomiting and asthenia [4, 6]. The majority of adverse events were mild (grade 1 or 2) and transient. Although grade 3 and 4 adverse events were rare, there was a relatively high incidence of dyspnoea, which was considered to be disease related. Preliminary data from a phase-II study with gefitinib showed an 18.7% response rate in 210 patients with NSCLC who had progressed after first- or second-line chemotherapy. In addition, it was reported that gefitinib was well tolerated; the most common side-effects were an acne-like skin rash and diarrhoea. The majority of adverse events were mild and transient. However, the current study presents the case of a patient with severe alveolar haemorrhage who had been given gefitinib. He was not permitted concomitant use of other drugs. After withdrawal of gefitinib, treatment with high doses of methylprednisolone and carbazochrome sodium sulphonate, and without any treatment of his cancer, his respiratory status gradually improved. Repeated examinations revealed no evidence of PCP, acid-fast bacilli, virus, fungi or malignancy as the cause of his acute lung injury. The BAL analysis showed haemosiderin-laden macrophages. Recent findings have suggested a role for the EGFR in tumour vascularisation [7]. Although the pathophysiological mechanisms of alveolar haemorrhage due to gefitinib remain unclear, the drug could act through inhibition of vascular endothelial growth factor expression.

To the best of the authors′ knowledge, this is the first reported case of an acute life-threatening alveolar haemorrhage in a patient with nonsmall-cell lung cancer who had been given gefitinib.

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