Fatal pulmonary toxicity in a patient treated with gefitinib for non-small cell lung cancer after previous hemolytic–uremic syndrome due to gemcitabine

Guilherme Rabinowits[a], Daniel Herchenhorn[b], Milton Rabinowits[b], Daniel Weatge[c] and Wilhermo Torres[d]

Gefitinib is a low-molecular-weight epidermal growth factor receptor tyrosine kinase inhibitor. To date, gefitinib has been administered to over 65 000 people worldwide. The most commonly reported adverse events were diarrhea, acne-like skin rash, nausea, vomiting and asthenia. Most of them were transient and mild in severity. Interstitial lung disease in patients who have been treated with gefitinib is uncommon and has recently been described with an estimated incidence rate of around 1%. We present here a case of fatal drug-induced pulmonary toxicity after therapy with gefitinib for metastatic non-small cell lung cancer. The patient had been treated with gemcitabine and cisplatin, and developed drug-induced hemolytic–uremic syndrome 6 months before gefitinib use. ***Anti-Cancer Drugs*** **14:665–668 © 2003 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2003, **14**:665–668

Keywords: gefitinib, non-small cell lung cancer, pulmonary toxicity

[a]Instituto Nacional de Câncer (INCA), [b]INCA and Oncologistas Associados Ltda, [c]Universidade Federal do Rio de Janeiro (UFRJ) and [d]INCA and Diagnose Laboratório de Patologia, Brazil.

Correspondence to D. Herchenhorn, Rua Barão de Lucena, 48/sala 20, 22260-020 Rio de Janeiro, RJ, Brazil.
Tel: +55 21 2539 0849; Fax: +55 21 2266 5306;
e-mail: oncobotadm@visualnet.com.br

Received 16 April 2003 **Revised form accepted** 17 June 2003

Introduction

Gefitinib is a selective low-molecular-weight epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor [1]. Interstitial lung disease (ILD) has been reported in a small minority of patients who have been treated with gefitinib [2]. In over 65 000 patients treated with gefitinib worldwide, ILD has recently been described with an estimated incidence rate around 1% [3]. The most commonly reported adverse events included diarrhea, acne-like skin rash, nausea, vomiting and asthenia. Most of them were transient and mild in severity [1].

We report a case of a 70-year-old female patient with metastatic non-small cell lung cancer (NSCLC) treated initially with gemcitabine and cisplatin, discontinued due to drug-induced hemolytic–uremic syndrome (HUS). This patient was treated with gefitinib 6 months later and after 2 months of its use she developed a lethal pulmonary toxicity.

Case report

A 70-year-old woman, with a long history of smoking was incidentally diagnosed stage IV NSCLC in May 1999, during workup for lumbar pain. Due to a lytic lesion, the patient was biopsied in the second lumbar vertebra, which revealed metastatic poorly differentiated adenocarcinoma. Computerized tomography (CT) scan of the chest revealed a left lung mass and mediastinal lymphadenopathy.

The patient received radiotherapy to the lumbar spine to a total dose of 20 Gy in 5 days, followed by chemotherapy with cisplatin and gemcitabine. Pre-medication consisted of granisetron and dexamethasone. She also received pamidronate and epoetin. In December 1999, she presented partial remission after seven cycles of chemotherapy, with clinical and radiological improvement of the lung mass and lymphadenopathy.

One year later, she developed cervical spine and right shoulder pain, and received radiotherapy to those areas with partial pain relief. In April 2001, a new chest CT scan revealed progressive disease. Pamidronate was substituted for zoledronic acid and five cycles of single agent gemcitabine were given. The last cycle of chemotherapy was in September 2001.

The patient was admitted to the hospital on day 43 of the last cycle of gemcitabine due to headache, confusion, vomiting, visual disturbance and mild disorientation. Magnetic resonance imaging of the brain was performed and showed evidence of ischemic lesion at the occipital lobe. Cerebral spinal fluid examination revealed high spinal fluid pressure. The patient developed atrial fibrillation and was admitted to a coronary care unit (CCU), receiving i.v. amiodarone over 2 days. At the CCU she developed severe high blood pressure, requiring nitroprusside administration. Complete blood cell counts and biochemistry showed progressive thrombocytopenia,

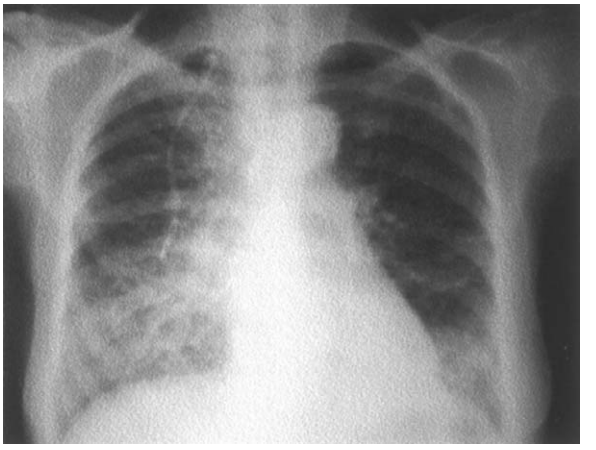
0959-4973 © 2003 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000089693.26177.3c

elevated LDH levels, hypoalbuminemia, reticulocytosis, and high BUN and creatinine levels. Diagnostic suspicion was hemolytic–uremic syndrome induced by gemcitabine. Platelet destruction and hemolysis were confirmed, and five plasmapheresis sessions were performed, on alternate days. In November 2001, after clinical and laboratory improvement, the patient was discharged from the hospital.

In February 2002, the patient experienced weight loss and worsening bone pain, with decreasing performance status, and gefitinib 250 mg once daily was initiated, as part of an expanded access use. Renal function and hematological evaluation were normal at that time. The patient developed a characteristic drug-related acne-skin rash and improvement of bone pain a few days later.

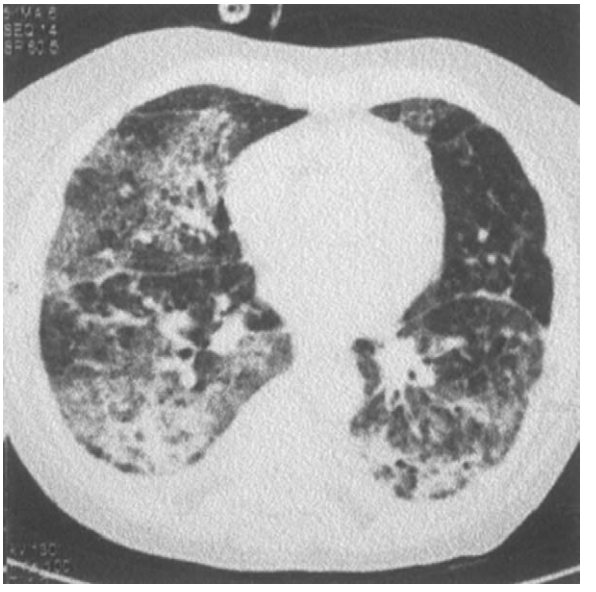
Two months later, the patient was hospitalized after a 2-week history of fatigue, progressive dyspnea and dry cough, which worsened over the last 72 h. She denied fever or chills. She was taking ranitidine, aspirin, laxative and gingko biloba. On physical examination, she was afebrile, acyanotic, anemic 3 + /4 + , tachypneic with 43 breaths/min, regular tachycardia, normal blood pressure and there were fine rales on her right lower third of the lung. Abdominal examination was normal. She received oxygen 3 l/min through a nasal catheter. Hematological exams disclosed a hemoglobin level of 9.7 g/dl, leukocyte count of 6300/μl with normal differential count and platelet count of 262 000/μl. Partial pressure of oxygen was 75.1 mmHg and partial pressure of CO_2 was 25.8 mmHg, with an oxygen saturation of 95% on oxygen 3 l/min by nasal catheter. Chest X-ray showed a diffuse pulmonary infiltrate (Fig. 1). Broad spectrum antibiotics and red blood cell transfusion were initiated. Symptoms improved, although tachypnea at rest remained. A chest CT scan was performed, revealing interstitial infiltrate with ground-glass pattern, mainly on both lower lobes; alveolar infiltrate on the medium lobe and discrete bilateral pleural effusion were also evident (Fig. 2). There was worsening of the respiratory function, in spite of the use of high-dose steroids, due to acute respiratory distress syndrome. Therefore, the patient was admitted to the intensive care unit requiring mechanical ventilation. Respiratory physiotherapy was initiated, gefitinib was discontinued and an open lung biopsy was performed. Histopathological examination showed the presence of mononuclear inflammatory infiltrate with slight septal thickening and focal fibroblastic infiltration forming intra-alveolar plugs; free macrophages and atypical hyperplasic areas in the alveolar lining could also be seen; the blood vessels were normal (Figs 3–5). Bacterial, fungal, viral and acid-fast bacillus cultures were all negative. There was worsening of her chest exam with bilateral diffuse rales. The patient developed hemodynamic instability and died 12 days after admission. Postmortem examination was not performed.

Fig. 1



Chest radiograph showing increased interstitial markings.

Fig. 2

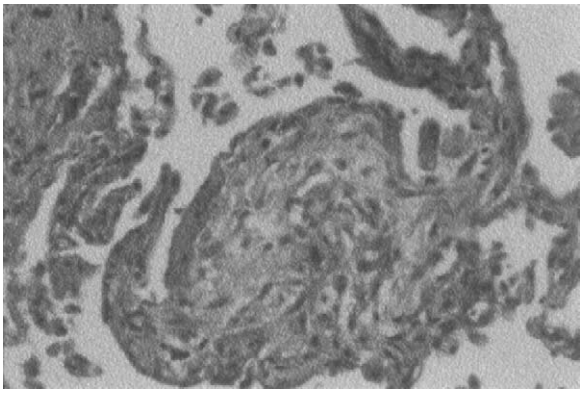


CT scan of the chest showing diffuse interstitial changes with a ground-glass appearance.

Discussion

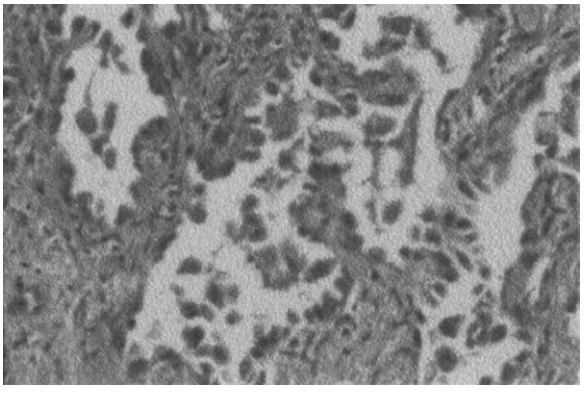
The prognosis of patients with NSCLC remains poor. Conventional combined chemotherapy regimens have been used for advanced disease, but with limited efficacy. Therefore, new molecular therapy has received a lot of interest due to its efficacy against NSCLC and possibly less toxicity. Gefitinib targets the EGFR, thereby

Fig. 3



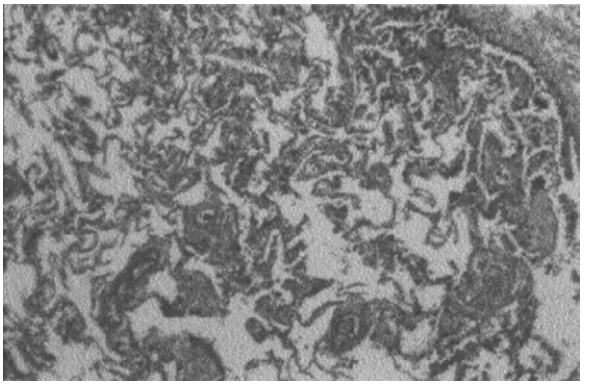
Fibroplasia causing focal septal enlargement (H & E, original magnification: × 100).

Fig. 4



Intense hyperplasia of alveolar lining (H & E, original magnification: × 400).

Fig. 5



General view of pulmonary parenchyma with mild septal fibrosis (H & E, original magnification: × 40).

inhibiting signal transduction pathways involved in tumor cell proliferation [1]. To date, gefitinib has been administered to over 65 000 people worldwide and its use has been approved for advanced, recurrent lung cancer in Japan since July 2002 [3,4]. It is considered as a well-tolerated oral drug; diarrhea and acne-like skin rash being the most common side effects, which are generally mild and reversible on cessation of treatment [1]. ILD has been reported in a small minority of patients who have been treated with gefitinib and, although new cases of pulmonary toxicity have been reported among advanced lung cancer patients using gefitinib in Japan [2], no causal relationship has been proved until now.

A phase I dose-escalation trial with 88 patients taking different doses of gefitinib for a variety of advanced solid malignant tumors reported grade 1/2 and 3 dyspnea as adverse effects in 12 and four patients, respectively. Grade 1/2 and 3 increased cough were also reported in 13 and one patients, respectively [1].

The incidence of ILD in patients treated with gefitinib in Japan was recently reported as 1.7% [2]. However, in over 65 000 patients worldwide who have received gefitinib, the reported incidence of ILD was around 1% and was approximately 0.3% in an extensive worldwide compassionate use program in over 28 000 patients, without any characteristic pattern of onset time, age, gender or previous treatments [3].

Two phase III studies, Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 and 2, investigated the efficacy and safety of gefitinib (250 and 500 mg once daily) versus placebo in combination with cisplatin plus gemcitabine and carboplatin plus paclitaxel respectively, in chemotherapy-naive advanced NSCLC patients (above 1000 in each study) [5,6]. There was no significant difference in patients receiving or not gefitinib with chemotherapy, with respect to incidence of ILD (0.9–1.1%) or other pulmonary events, such as pneumonia, dyspnea or cough [3].

Gemcitabine is also a drug that has already been associated with lung injury. Dyspnea has been usually seen within hours to days of starting the treatment and varies from mild to a fatal acute respiratory distress syndrome [7,8]. The mechanism of action is unclear, although a systemic capillary-leak syndrome has been suggested as the pathogenic mechanism. This syndrome is caused by sudden, reversible capillary hyper-permeability with rapid extravasation of plasma from intravascular to the interstitial space, leading to a rapidly developing edema, weight gain, hypotension, hemoconcentration and hypoproteinemia [8,9]. Although there is

no reported case of pulmonary toxicity after 6 months of gemcitabine use, symptoms and imaging features in this case, such as ground-glass opacity, thickened septal lines and reticular opacities, symmetric or not, were similar to those described on gemcitabine-induced lung injury [10].

It is important to mention that this patient had the diagnosis of gemcitabine-induced HUS 5 months before the pulmonary event. Gemcitabine is a pyrimidine analog of deoxycytidine with a similar chemical structure and mechanism of action as cytarabine. It has been shown to be a highly active agent for many solid and hematological malignancies, and is relatively well tolerated, with myelossupression as the main toxicity [7,8,11]. There have been a few confirmed cases of gemcitabine-associated HUS and the reported incidence was about 0.015% [12]. Treatment of this rare syndrome is not uniform. In this case, five sessions of plasmapheresis were done with rapid improvement of laboratorial exams and symptoms, although a mild increase in BUN persisted. This patient presented with HUS 43 days from the last dose of gemcitabine. It has been described that the interval between the last dose of gemcitabine and the development of HUS ranged from 1 day to several months. The mechanism of action is still unclear, but it has been suggested that endothelial injury is the central feature [13].

Amiodarone was also administered to this patient and pulmonary toxicity has been described as the most serious adverse reaction of this drug, which occurs in 5–15% of patients [14]. This pulmonary toxicity correlates more closely with total cumulative dose than with serum drug levels [14]; therefore, it usually occurs after several months of amiodarone therapy and not after a short use for restoration of sinus rhythm after acute atrial fibrillation as in this case.

The diagnosis of drug-induced lung injury is one of exclusion. There are multiple recognized mechanisms by which antineoplastic drug-induced lung injury may manifest: oxidized lung injury, direct cytotoxic effect on alveolar capillary endothelial cells, deposition of phospholipids within pulmonary cells, particularly the alveolar macrophage, immune-mediated injury, bronchiolitis obliterans with organizing pneumonitis, bronchospastic changes, pleural effusions, pulmonary venous-occlusive disease with vasculitis and thromboembolic disease [13]. The patient had symptoms, imaging and laboratory exams compatible with diffuse ILD, and a lung biopsy compatible with a drug-induced reaction.

Any causal relationship with gefitinib remains unknown and therefore it is difficult to comment on any potential mechanism of pulmonary toxicity. The possibility of an interaction between gefitinib and gemcitabine in this drug-related pulmonary event cannot be proved at this moment. Although most of the drug-induced pulmonary toxicity is resolved with discontinuation of the drug and the use of high-dose steroids [11], there was no consistent clinical benefit with those measures in this case.

It is important to be aware of this rare syndrome of dry cough, progressive dyspnea and interstitial infiltrates that can appear during the administration of gefitinib. However, these adverse events should be considered in the context of the overall toxicity profile of the treatment and serious nature of NSCLC. Indeed, while vigilance for pulmonary toxicity is mandatory, the small risk of developing ILD-type events should not prevent patients from receiving benefit from this type of agent.

Acknowledgments

The authors thank Hedilene Cardoso, Oncology Medical Manager of AstraZeneca Brazil, for assistance with the updated information about the incidence of pulmonary events in advanced lung cancer patients using the new oral drug gefitinib.

References

1 Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, *et al.* Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002; **20**:4292–4302.
2 Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; **361**:137–139.
3 Ochs JS. AstraZeneca Pharmaceuticals. Personal communication.
4 Twombly R. Cancer spectrum: despite concerns, FDA panel backs EGFR inhibitor. *J Natl Cancer Inst* 2002; **94**:1596–1597.
5 Giaccone G, Johnson DH, Manegold C, Scagliotti GV, Rosell R, Wolf M, *et al.* A phase III clinical trial of ZD1839 (Iressa®) in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced non-small cell lung cancer. *Ann Oncol* 2002; **13**:4.
6 Johnson DH, Herbst R, Giaccone G, Schiller J, Natale RB, Miller V, *et al.* ZD1839 (Iressa®) in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced non-small cell lung cancer: results from a phase III clinical trial (INTACT 2). *Ann Oncol* 2002; **13**:468.
7 Rosado MF, Kett DH, Schein RMH, Baraona FJ, Sridhar KS. Severe pulmonary toxicity in a patient treated with gemcitabine. *Am J Clin Oncol* 2002; **25**:31–33.
8 Gupta N, Ahmed I, Steinberg H, Patel D, Nissel-Horowitz S, Mehrotra B. Gemcitabine-induced pulmonary toxicity: case report and review of the literature. *Am J Clin Oncol* 2002; **25**:96–100.
9 De Pas T, Curigliano G, Franceschelli L, Catania C, Spaggiari L, de Braud F. Gemcitabine-induced systemic capillary leak syndrome. *Ann Oncol* 2001; **12**:1651–1652.
10 Boiselle PM, Morrin MM, Huberman MS. Gemcitabine pulmonary toxicity: CT features. *J Comput Assist Tomogr* 2000; **24**:977–980.
11 Vander Els NJ, Miller V. Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. *Chest* 1998; **114**:1779–1781.
12 Walter RB, Joerger M, Pestalozzi BC. Gemcitabine-associated hemolytic–uremic syndrome. *Am J Kidney Dis* 2002; **40**:E16
13 Cooper JA, Zitnik R, Matthay RA. Mechanisms of drug-induced pulmonary disease. *Ann Rev Med* 1988; **39**:395–404.
14 Martin II W, Rosenow III EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (part 1). *Chest* 1988; **93**:1067–1075.