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Gefitinib ('Iressa', ZD1839): the patients' experience

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Abstract

Following the demonstration of encouraging antitumour activity and favourable tolerability by the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in phase I studies, an Expanded Access Programme (EAP) allowed gefitinib to be given to patients with advanced non-small-cell lung cancer (NSCLC) who had exhausted all other treatment options. The EAP case reports presented here demonstrate the remarkable effect that gefitinib can have on individual patients with a range of clinical characteristics, including brain and bone metastases, poor performance status and advanced age. Gefitinib not only shows antitumour activity against primary tumours and metastases, it also leads to meaningful improvements in disease-related symptoms and quality of life for many NSCLC patients.

Keywords: Gefitinib; Iressa; ZD1839; Case studies; Epidermal growth factor receptor; EGFR

1. Introduction

Following the demonstration of the encouraging antitumour activity and favourable tolerability of the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib ('Iressa', ZD1839) in phase I studies and prior to regulatory approval, gefitinib was made available on a compassionate-use basis for patients with advanced non-small-cell lung cancer (NSCLC) who had exhausted all other treatment options and were not eligible for clinical trials. The introduction of the gefitinib Expanded Access Programme (EAP) enabled more than 37,000 patients with advanced NSCLC in more than 70 countries to receive gefitinib treatment by June 2003. The extensive clinical experience generated by the EAP will provide additional essential information to help to optimise the use of this novel biologically targeted agent.

The EAP has provided many examples of patients who have responded well to gefitinib, including those with different clinical characteristics such as widely metastatic disease or poor performance status (PS), and elderly patients. The case reports presented here represent examples of patients with each of these characteristics.

2. Metastatic disease

Despite initial doubts that gefitinib would be able to cross the blood-brain barrier, there have been numerous reports of patients in whom brain metastases have regressed following gefitinib treatment [1,2]. One such case is that of a 55-year-old male diagnosed with stage IIIb adenocarcinoma with mediastinal lymph node involvement in April 2000 [3]. He was initially treated with carboplatin/paclitaxel and radiotherapy. During treatment, the patient developed a large pulmonary embolus and was admitted to the intensive care unit. At this time a magnetic resonance imaging (MRI) scan confirmed the presence of brain metastases, which were initially treated with whole-brain irradiation. He was then treated with gemcitabine followed by temozolomide, an agent that crosses the blood-brain barrier. A few months later, treatment with platinum and irinotecan was started. The lung and adrenal gland showed some response to treatment but the brain metastases continued to progress. In December 2001, a lumbar puncture and cerebrospinal fluid cytology demonstrated carcinomatous meningitis and, despite a trial of intrathecal chemotherapy, his overall functional status

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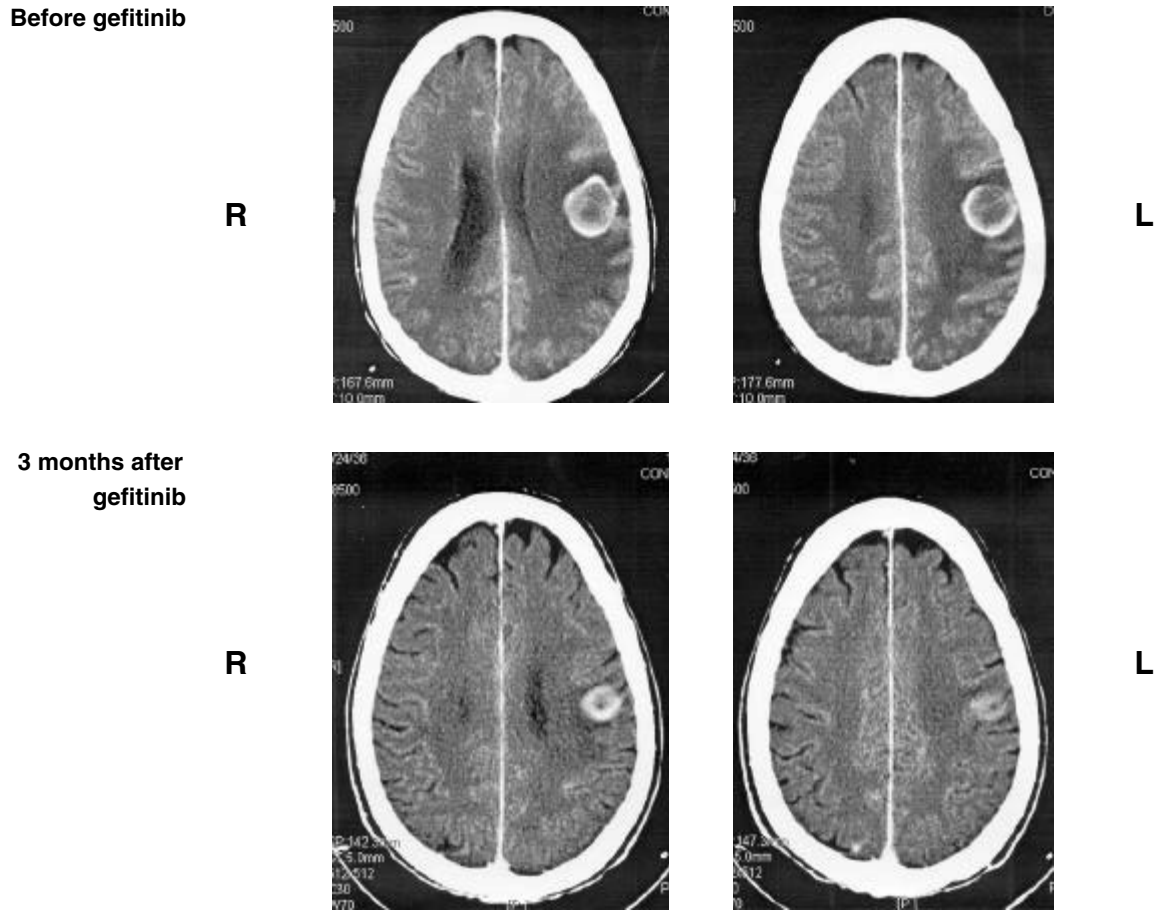

Fig. 1. CT scan of a brain metastasis from NSCLC responding to gefitinib therapy. This patient had been pretreated with three lines of chemotherapy including platinum and taxanes, and received gefitinib after whole-brain radiotherapy failure. Reproduced with permission from: Cappuzzo F, Calandri C, Bartolini S, Crino L. ZD1839 in patients with brain metastases from non-small-cell lung cancer (NSCLC): report of four cases. *Br J Cancer* 2003, **89**, 246–247.

worsened. Gefitinib 250 mg/day was started in January 2002. The patient showed symptomatic improvement at a follow-up visit in February, which continued to be observed at monthly visits. In June, an MRI scan of the brain showed dramatic shrinkage of all the metastases in the brain, and computed tomography (CT) scans showed disappearance of the lung tumour and shrinkage of adrenal metastases (Fig. 1). This response to gefitinib was accompanied by an overall improvement in the patient's general well-being.

Patients with NSCLC often experience bone metastases; gefitinib has proven to be effective at treating these metastases as well as the primary tumours. For example, a 59-year-old woman with bone metastases, who had previously received chemotherapy, experienced benefit with gefitinib [4]. In November 2000, she was diagnosed with stage IV adenocarcinoma of the lung with a metastasis to the right femur confirmed on an MRI scan. The patient reported being breathless and required help to get dressed. Following pleurodesis for a pleural effusion, the patient received six cycles of cisplatin/gemcitabine (December 2000 to April 2001). In April 2001, a CT scan confirmed stable disease with pleural thickening along the right lateral chest wall, blunting of the right costaphrenic angle, and a persistent right peritracheal density. In June 2001, the patient started gefitinib treatment and showed increased symptomatic improvement at each monthly visit. In September 2001, a bone scan revealed that the metastasis in her right femur had shrunk. By December 2001, the only signs of disease were a small pleural effusion with a calcified pleural density. A CT scan in June 2002 confirmed further resolution of air-space opacities in the right lower lobe and the right hemithorax. The only reported side effect of gefitinib was skin rash. In September 2002, the patient reported being able to run and work in the garden [4].

3. Poor performance status

Poor PS is a well-recognised prognostic factor for a poor outcome in patients with NSCLC [5]. However, there are several examples of patients with poor PS who have responded well to gefitinib. A 52-year-old woman with

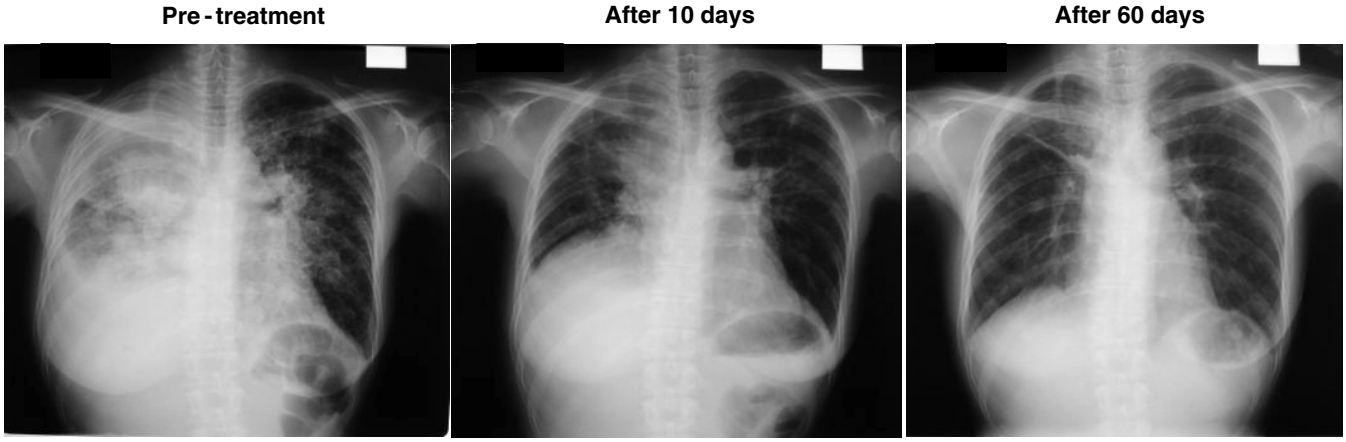

Fig. 2. Chest X-ray of a patient with adenocarcinoma of the lung, showing the effects of treatment with gefitinib. Reprinted from *Lung Cancer*, vol. 40: Fujiwara K, Kiura K, Ueoka H, Tabata M, Hamasaki S, Tanimoto M. Dramatic effect of ZD1839 ('Iressa') in a patient with advanced non-small-cell lung cancer and poor performance status. Pages 73–76, Copyright (2003), with permission from Elsevier Ireland Ltd.

adenocarcinoma of the lung and metastases to the lung and brain and a PS (Eastern Cooperative Oncology Group [ECOG]) of 4, who had previously received chemotherapy, showed a complete response and improvement in PS with gefitinib [6]. This patient had been diagnosed in July 1999. She initially responded well to cisplatin-based chemotherapy; however, the disease subsequently progressed and failed to respond to salvage chemotherapy. She later received whole-brain irradiation for asymptomatic brain metastases. In November 2001, the patient had metastatic lesions in the lungs and brain, a PS of 4, and was unable to carry out any self-care, being confined to bed due to dyspnoea. By Day 10 of oral gefitinib 250 mg/day, a chest X-ray showed marked regression of multiple pulmonary metastases and improvement of both her lymphangitis carcinomatosa and a massive right pleural effusion (Fig. 2). Her dyspnoea gradually improved, breath sounds became clearly audible in the right lung and her oxygen saturation (SpO_2) increased from $\leq$90% to 96% on room air. Ring-enhanced metastases in her brain disappeared. Gefitinib administration was interrupted after 8 weeks due to grade 2 skin rash on her neck and face, but she was successfully rechallenged 2 weeks later, although grade 1 rash still remained. A month after starting gefitinib treatment, the patient was discharged from hospital without the need for supplemental oxygen. She continued to take gefitinib 250 mg once daily, and resumed full-time work. Seven months after starting treatment, the patient had a PS of 0 and no lung-cancer-related symptoms [6].

4. Elderly patients

Advanced age in patients with NSCLC is often associated with a poor PS and multiple comorbidities. Elderly patients need medications that are easy to take, with limited adverse events and a low risk of drug interaction. Gefitinib appears to meet these criteria, and has been shown to be effective and well tolerated in the elderly [7]. A case that demonstrates this is a 70-year-old woman who initially presented with a 2-month history of haemoptysis and a PS of 1. In July 1998, she underwent an uncomplicated right middle lobectomy with mediastinal lymph node sampling. Histological examination revealed poorly differentiated squamous-cell carcinoma with some mucin-secreting adenocarcinoma at the periphery, while a separate pretracheal lymph node showed a focus of metastatic adenocarcinoma. A CT scan in November 2001 showed progressive disease with multiple liver metastases, and six cycles of chemotherapy (mitomycin, vinblastine, cisplatin) were administered. Cisplatin was replaced with carboplatin in the last cycle due to mild peripheral neuropathy. After three and six cycles, CT scans demonstrated stable disease with a concomitant good symptomatic response. The patient remained well until December 2002, when she developed a dry cough and right-sided pleuritic chest pain. In February 2003, she had deteriorated significantly with increasing fatigue (only able to shower with great difficulty), exertional dyspnoea, dry cough, right upper quadrant pain and weight loss. Her PS was 2–3 and she had to be wheeled into the clinic by her family. CT scans of the chest and abdomen confirmed progressive disease. Gefitinib was applied for on a compassionate-use basis as her PS precluded the use of second-line chemotherapy; treatment was initiated in March 2003. After 1 month she showed improvement in all facets of her disease and was able to walk into the clinic. At this time, her PS had improved to 1–2, her cough, dyspnoea and energy had improved, she had no right upper quadrant pain and her weight was stable. The only significant adverse events reported were diarrhoea from Day 4 (which subsequently resolved), a mild-to-moderate acneiform rash that developed on Day 8 and dry skin. A CT scan at 3 months showed a partial tumour response, including reduction in the number of liver metastases (Fig. 3). The patient kept a daily diary of her symptoms from initiation of her therapy

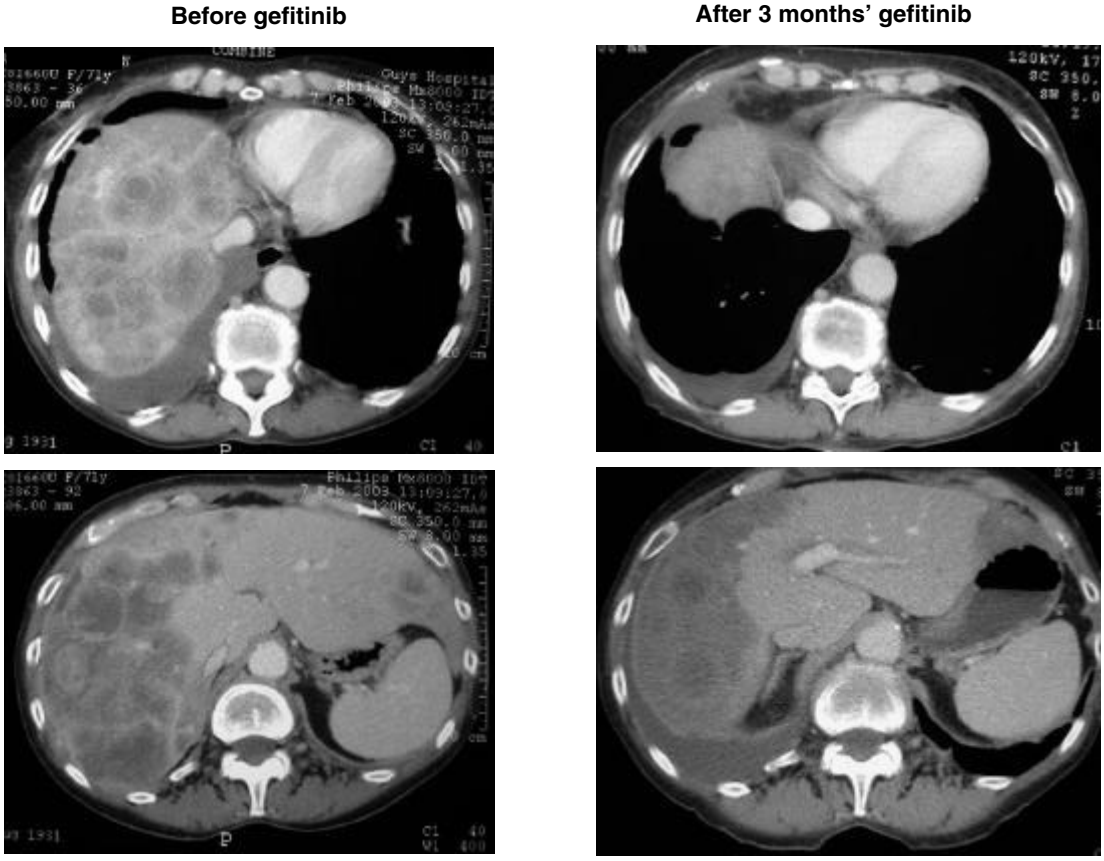

Fig. 3. CT chest and abdomen scans of a patient with NSCLC and liver metastases, before and after treatment with gefitinib. Reproduced with permission from Dr Peter Harper.

Table 1
Patient diary on gefitinib 250 mg/day (Reproduced with permission from Dr Peter Harper)

Day 1	Sleepless night, no pain, just cough.
Day 3	Good night, only cough woke me, more life in me today.
Day 6	Good night, but had another hernia attack at 2 am. Otherwise had a comfortable day, started to feel a lot stronger. Only had one coughing bout, which left me without a voice.
Day 8	Fairly good night, but hernia attack woke me again, loose bowels again once at 04:35 and once at midday. Noticed small amount of rash on face. But also felt I was not so breathless, felt good.
Day 9	Good night, woke with rash of face, good day, did quite a lot of 'pottering' about, even toured the garden. Certainly not so breathless, felt good.
Day 16	Very good night, Mother's Day good day. Saw all the children. Felt strong. Went to bed, feeling very tired. Rash on face felt sore today.
Day 23	Very good night, no headache, followed by good day. Had visit from district nurse, 'just to get to know you'. I actually did some ironing today! Rash on face.

(Table 1). She showed continued improvement at monthly visits; in July 2003, her PS was 1 and she was planning a holiday to Europe.

5. Conclusions

These case studies, and many other reports, demonstrate the remarkable effect that gefitinib can have on individual patients with a range of clinical characteristics. Not only does gefitinib show benefit in the measurable reduction of primary tumours, it may also be effective in the treatment of bone and liver metastases and can lead to the shrinkage of brain metastases. Perhaps most importantly, gefitinib treatment commonly results in meaningful improvement in disease-related symptoms and quality of life for many NSCLC patients, allowing them to feel that they can lead a normal life. These examples of the potential benefits of gefitinib support its continued use in patients who have exhausted all other treatment options.

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