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Clinical Study

Gefitinib ('Iressa', ZD1839) is active against brain metastases in a 77 year old patient

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Summary

This report highlights the case of a symptomatic 77-year-old non-smoking female patient who was diagnosed with advanced non-small-cell lung cancer (NSCLC), metastatic to the liver and contralateral lung. After tumor progression in the liver and lung following polychemotherapy, multiple diffuse brain and cerebellar metastases were apparent. Oral treatment with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa') 250 mg/day resulted in progressive and durable symptom relief, and improvements in quality of life and performance status. Reductions in the size of the primary pulmonary tumor and brain, cerebellar, and liver metastases were observed. Furthermore, gefitinib was well tolerated with an absence of adverse events. These results provide evidence that oral gefitinib is active in patients with advanced NSCLC and central nervous system metastases.

Introduction

The symptoms and treatments of non-small-cell lung cancer (NSCLC) can be severe and debilitating for the patient, and may impact on quality of life. Approximately 30–40% of patients with NSCLC present with metastases; the most common clinically apparent sites of spread are the liver, bones, adrenal glands, and central nervous system (CNS). CNS or brain metastases may manifest with symptoms such as non-specific headache, a change in mental status, focal or generalized seizures, or localized weakness [1].

The epidermal growth factor receptor (EGFR) is expressed or highly expressed in a wide range of tumor cells, and expression correlates with disease progression, resistance to chemotherapy, and tumor invasion [2]. The orally active EGFR tyrosine kinase inhibitor (EGFR-TKI) gefitinib ('Iressa', ZD1839) blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. In 2 Phase II trials (IDEAL ['Iressa' Dose Evaluation in Advanced Lung cancer] 1 and 2) of gefitinib monotherapy in patients with advanced NSCLC who had received prior chemotherapy, gefitinib (250 and 500 mg/day) was well tolerated and provided rapid and durable symptom relief, which correlated with tumor response and improved overall survival [3,4]. Patients who were ineligible for these clinical trials, had failed previous chemotherapy, or were unable to tolerate further chemotherapy were able to receive gefitinib as part of a global compassionate-use program. From April to December 2002, seven patients with advanced NSCLC received gefitinib on a compassionate-use basis at our institution. Of these, six patients showed no evidence of brain metastases at diagnosis or during treatment, whereas one patient developed brain metastases and is described herein.

Case report

We report the case of a 77-year-old non-smoking female patient admitted to our institution on 16 December 2001 with severe chronic cough, asthenia, and dyspnea at rest. During the 2 months prior to admission, the patient had mild dyspnea on exertion, a cough that was occasionally productive, and a weight loss of 5 kg. An X-ray of the chest and a computed tomography (CT) scan showed large opacities of the upper lobe of the left lung with mediastinal lymph node involvement. A fiber-optic bronchoscopic examination showed partial airway obstruction by an erythematous and friable 'tumor' in the upper left bronchus. Bronchial brushing, bronchoalveolar lavage, and bronchial biopsies were performed. Cytologic and histologic examinations (hematoxylin and eosin staining) of the specimens confirmed a poorly differentiated adenocarcinoma of the left upper lobe of the lung that was locally advanced and metastatic (liver and contralateral lung; Figure 1). This symptomatic patient was initially treated with age-adjusted polychemotherapy regimens (first-line vinorelbine 15 mg/m^2 and cyclophosphamide 300 mg/m^2 on a weekly regimen for 5 weeks and, after 3 weeks' rest, second-line irinotecan 70 mg/m^2 and gemcitabine 500 mg/m^2 on a weekly regimen for 4 weeks; January–March 2002). In March 2002, two-and-a-half months after diagnosis, the patient started anticoagulation therapy (warfarin) for right leg venous thrombosis with suspicion of peripheral pulmonary embolism (severe dyspnea). After this time, the patient's general condition deteriorated and she complained of a headache. Tumor progression was documented in the lung as well as in the liver (Figure 2), and a CT scan showed multiple diffuse brain (Figure 3a) and cerebellar (Figure 3b) metastases. Once-daily oral treatment with 250 mg gefitinib was initiated in April

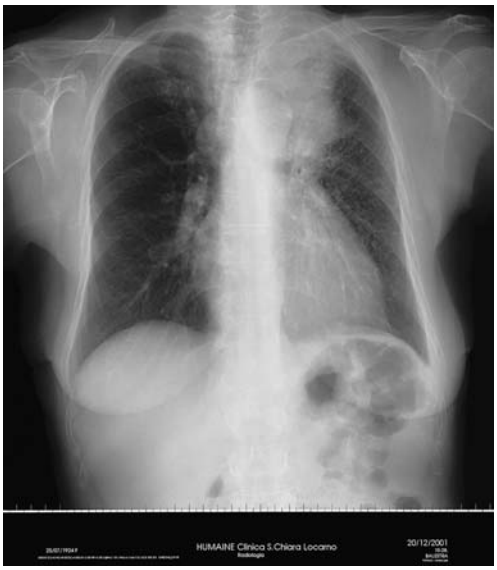

Figure 1. Chest X-ray showing poorly differentiated adenocarcinoma of the left upper lobe of the lung.

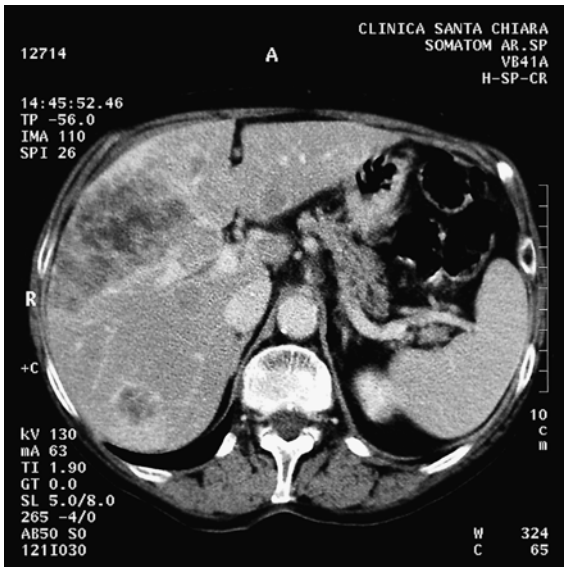

Figure 2. Computed tomography scan showing tumor progression in the liver.

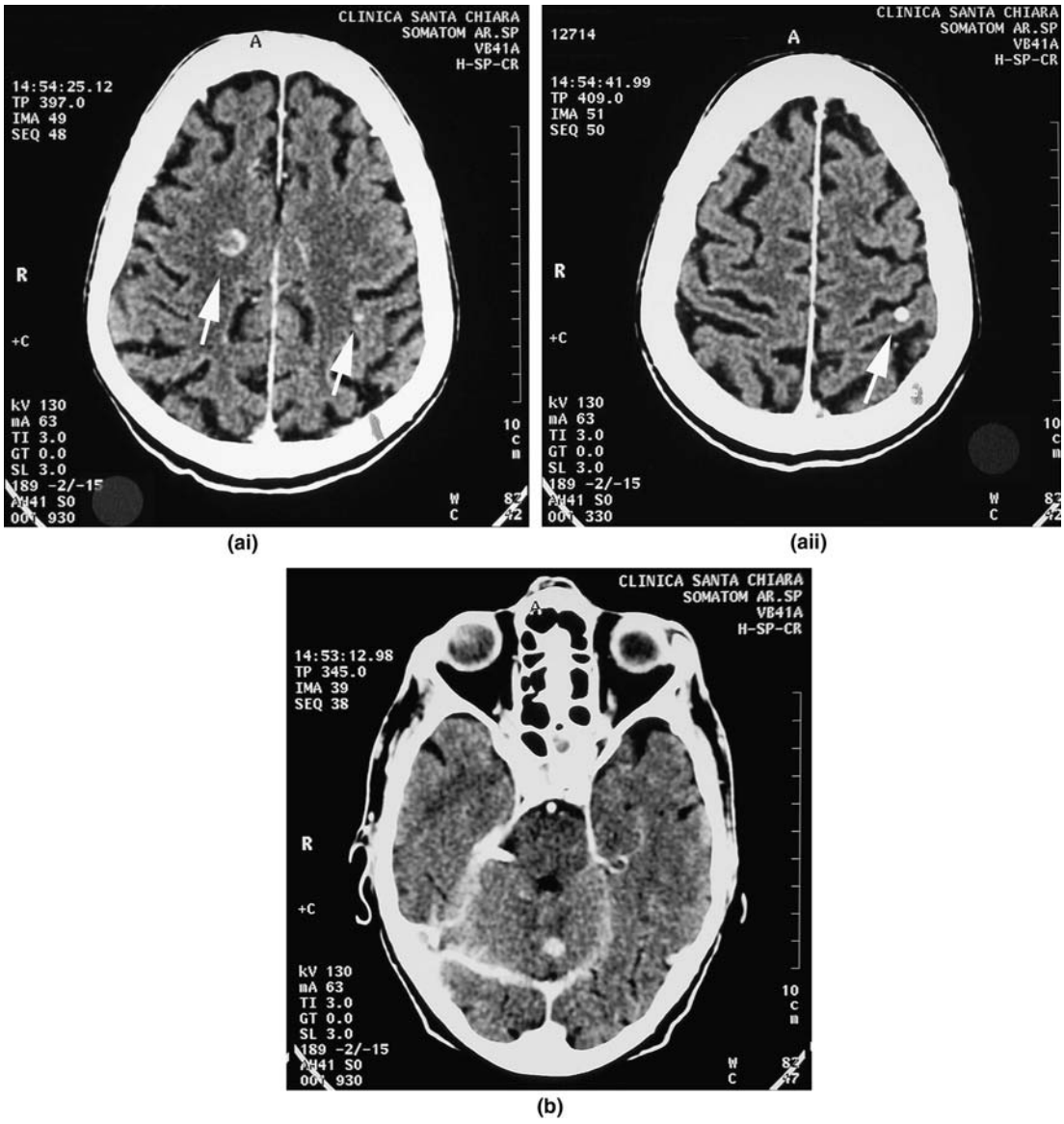

Figure 3. Computed tomography scan showing multiple diffuse (a) brain, and (b) cerebellar metastases.

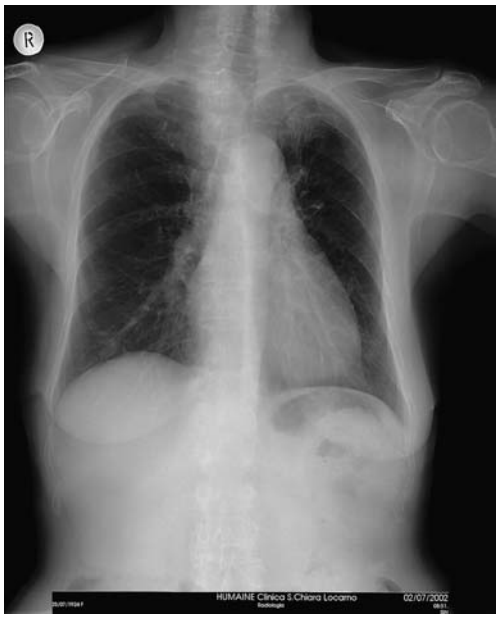

Figure 4. Chest X-ray showing a significant reduction in the size of the primary pulmonary tumor following gefitinib treatment.

2002 on a compassionate-use basis. At the start of gefitinib treatment, her World Health Organization (WHO) performance status was 2. After 2 months (June 2002), progressive relief of fatigue, cough, and pain, and significant reductions in size of the primary pulmonary tumor (Figure 4) and brain (Figure 5a), cerebellar (Figure 5b), and liver (Figure 5c) metastases were observed, and confirmed by chest X-ray and CT scan. The duration of symptom relief was approximately 7 weeks, and during this time the patient's quality of life improved, her WHO performance status was 0, and she was able to resume her normal activities at home.

Gefitinib treatment was administered for 5 months and during this time the patient developed cranial neuropathy of the left VII to IX nerves with herpes zoster virus, which rapidly regressed after 10 days' administration of acyclovir (gefitinib was stopped for 6 days). No evidence of leukopenia or thrombocytopenia was found during treatment with gefitinib, and no other adverse events were recorded. The patient died 9 months after diagnosis (September 2002; 5 months after start of

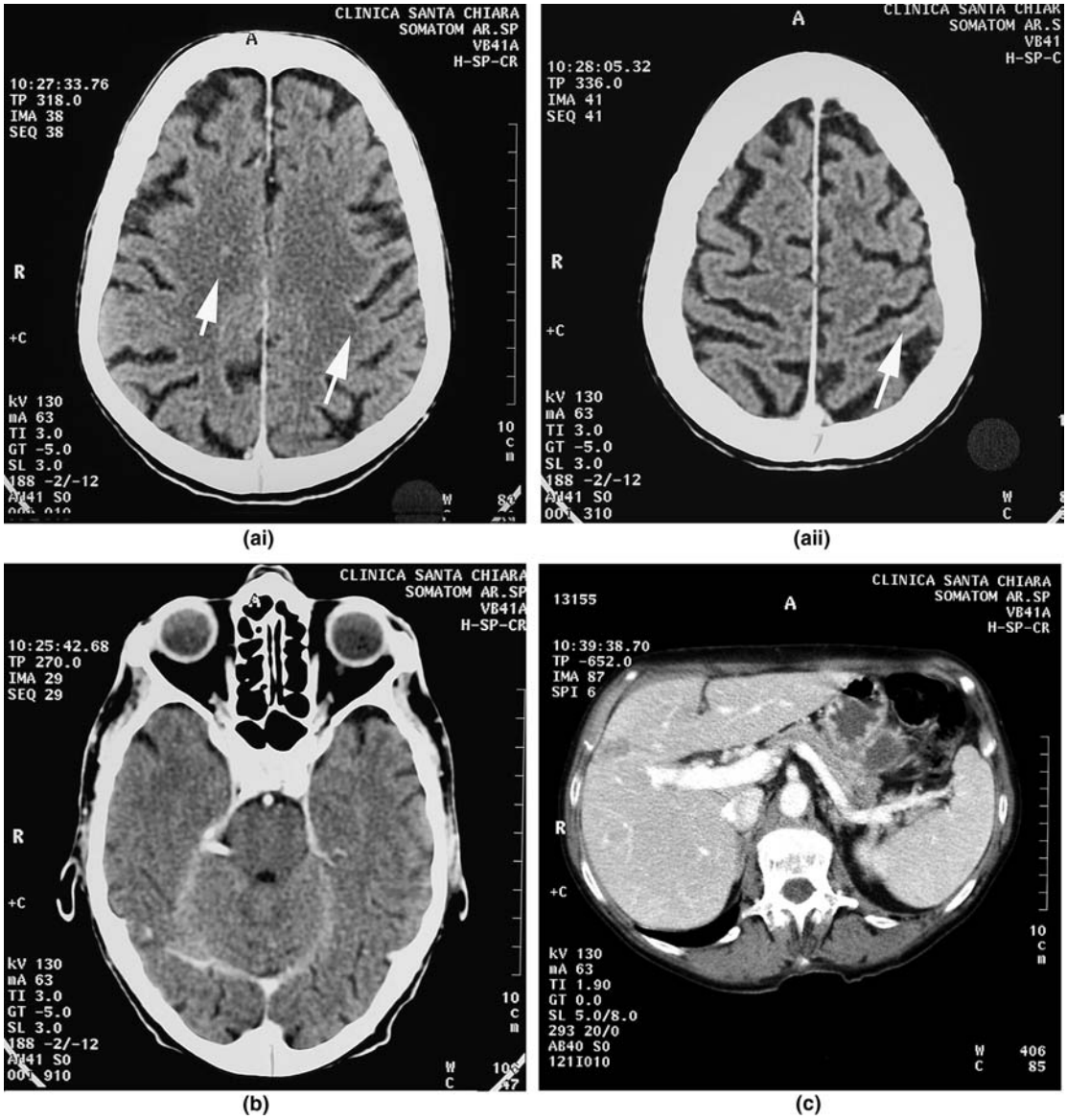

Figure 5. Computed tomography scan showing a significant reduction in (a) brain, (b) cerebellar, and (c) liver metastases.

gefitinib treatment) due to rapid progressive liver disease.

Discussion

Patients with advanced NSCLC suffer severe and debilitating symptoms and often have compromised quality of life. In general, disease-related symptoms result from tumor growth and spread, systemic effects, and metastasis. In advanced NSCLC, there is an unmet need for novel, well-tolerated agents that improve disease-related symptoms without further compromising quality of life. One such agent is the EGFR-TKI gefitinib. Recent clinical results from 2 Phase II trials of gefitinib monotherapy in pretreated patients with advanced NSCLC demonstrate that gefitinib has clinically significant antitumor activity, and rapid and durable symptom relief. In this case report of a patient with metastatic NSCLC with CNS metastases, who received gefitinib as part of a compassionate-use program, durable symptom relief was reported. Furthermore, gefitinib appeared to demonstrate activity against the primary pulmonary tumor and the brain and liver metastases, and was well tolerated.

In conclusion, the results of this case report provide evidence that orally administered gefitinib is active in symptomatic patients with NSCLC and CNS metastases and may be an important novel treatment option for these patients. Further clinical studies are required to confirm the use of gefitinib in this clinical setting.

References

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