



Case report

Advanced lung adenocarcinoma in an EGFR-positive patient treated with Erlotinib for 52 months



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ABSTRACT

The authors present a case of a 53-years-old non-smoker Caucasian female who was diagnosed with lung adenocarcinoma (stage IA) and underwent surgical resection in 2002. Five years later, the tumor relapsed (stage IV disease) and she initiated chemotherapy with carboplatin, gemcitabine and bevacizumab as a first-line therapy. Despite partial remission after four cycles, this regimen was discontinued due to unacceptable toxicity. In 2008, the disease progressed and the patient was started on Erlotinib as second-line treatment. The patient had a sustained partial remission which she maintains at present – 52 months after initiation of Erlotinib. Molecular testing performed on the primary lung tumor revealed an Epidermal Growth Factor Receptor (EGFR) gene mutation (deletion in exon 19).

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1. Introduction

In Europe, non-small cell lung cancer (NSCLC) accounts for approximately 85–90% of malignant lung neoplasms and this type of cancer is more prevalent in males [1] but is increasing significantly in women [2]. According to an European forecast study for 2012, lung cancer will be the first cause of death among women in Poland and the United Kingdom [3].

Until 2009, platinum-based doublets chemotherapy was the accepted standard of care for first-line treatment of advanced NSCLC. The response rate was 30% with a median progression-free survival (PFS) and an overall survival (OS) of 6.4 and 10–12 months, respectively [4,5].

Since 2004, several studies have shown that patients with Epidermal growth factor receptor (EGFR) mutations are the best predictor of response to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib [5], fact that has changed dramatically the paradigm of advanced NSCLC treatment.

EGFR is a transmembranal glycoprotein detectable in 80–85% of NSCLC which has a cytoplasmatic domain with TK activity [2,6]. Multiple ligands bind this receptor to initiate signal transduction cascade leading to cell proliferation, antiapoptosis, angiogenesis, invasion and metastasis [7]. Certain somatic mutations in the TK domain of EGFR gene, mostly in exon 19 and 21 are “activating”,

meaning that binding of erlotinib or gefitinib to this domain prevents cancer progression [5,6,8]. Such mutations are more frequent among women, patients with adenocarcinoma, non-smokers and East Asians individuals [5,9,10].

Currently, TKIs are considered the best first-line of treatment for patients EGFR-positive with advanced NSCLC, improving PFS and quality of life with less toxicity [11,12] and also play an important role in second-line setting with similar efficacy to Docetaxel and Pemetrexed but with the advantage of oral administration and better tolerability [13].

Therefore, assessment of EGFR mutation status is crucial to identify patients who will respond to TKIs [14]. Furthermore, recent studies have shown that EGFR expression is not stable during metastatic progression, fact that has important clinical implications and must be considered before starting this therapy [14].

Another emerging issue concerning TKI treatment is that most patients with advanced NSCLC and activating EGFR mutations experience marked improvement but eventually develop progression of disease within a median of 6–12 months [15,16].

2. Case report

In June 2002 a 53-yr-old Caucasian female was referred to our Pulmonary Oncology consultation with a six-month history of recurrent respiratory infections characterized by cough with mucous sputum. She had no fever, chest pain or dyspnea and also denied constitutional symptoms. Chest radiograph showed a non-calcified 2 cm nodule in the right upper lobe and chest CT scan

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confirmed the presence of a spiculated nodule with 2.5 cm in the apical segment of right upper lobe. She was a housewife, did not have drinking or smoking habits, though she was a passive smoker. She had undergone total hysterectomy with bilateral salpingo-oophorectomy due to uterine fibromatosis and had a history of chronic constipation. She denied taking medication on a regular basis and drug allergies. Her family history was unremarkable. On physical examination, she was moderately obese (BMI 35.1 kg/m²), hemodynamically stable and had no signs of respiratory distress (RR 16 cpm and SpO₂ 98% on room air). Cardiopulmonary auscultation was normal as the remaining exam was unremarkable.

Because percutaneous transthoracic biopsy was technically unfeasible, she underwent thoracic surgery. Extemporaneous histological exam revealed lung adenocarcinoma with papillary pattern areas and bilobectomy (right and middle lobe) was then performed. Final pathological staging was pT1N0M0, stage IA.

In May 2007 despite asymptomatic, thoracoabdominal CT scan showed diffuse pulmonary metastasis and a lobulated lesion in the right lower lobe (RLL) (Fig. 1A). The patient was included in an international multicenter trial and was started on carboplatin, gemcitabine and bevacizumab every 3 weeks. Despite partial remission after 4 cycles (Fig. 1B), therapy was discontinued due to unacceptable hematologic toxicity.

One year later as thoracoabdominal CT scan revealed progressive disease (Fig. 1C) we decided to send surgically resected tissue for molecular testing. Evaluation of EGFR mutation, KRAS mutation, and ALK gene rearrangement were performed and revealed a deletion in exon 19 (Del 2235-2249). The patient was

started on oral Erlotinib (150 mg/day). By the second week of treatment she developed a severe (grade 3) facial rash that improved to grade 1 with oral doxycycline 100 mg and topical treatment. At present she is asymptomatic and maintains partial remission (Fig. 1D). Due to the excellent response and manageable toxicity, our patient is still on treatment with Erlotinib after 52 months. In order to monitor treatment's response and detect possible side-effects, a clinical and imagiological (chest X-ray or Chest CT scan) evaluation will be performed every month.

3. Discussion

Therapy of advanced NSCLC has changed dramatically after the development of TKIs. Response to this therapy depends on the presence of EGFR gene mutations in exons 19 and 21 [9,10]. In Caucasians, these mutations predominate in females, non-smokers and adenocarcinoma histology [5]. Considering both clinical and histological characteristics of our patient, there was an increased probability of EGFR mutation positivity.

A recent study showed that 50% of patients with EGFR mutation-positive primary lung tumors lose the mutation in metastasis and that discordance rate of EGFR expression between primary tumor/metastases can reach 27% [14]. In view of current knowledge, the analysis of EGFR mutation status in the primary tumor may be inadequate for planning the use of TKIs for advanced NSCLC, reason why tissue sampling from distant metastases must be pursued to accurately determine EGFR mutations before treatment [14]. Fortunately, although this procedure was not performed,

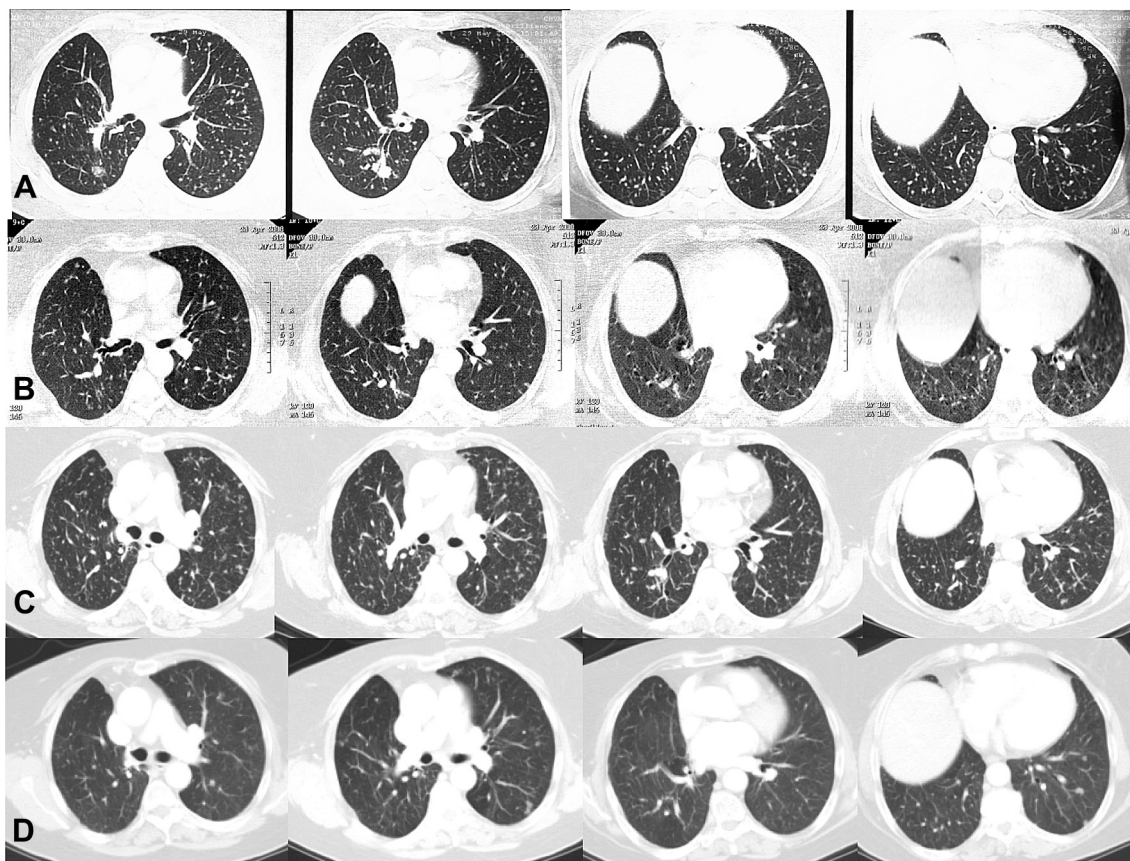


Fig. 1. (A) Chest CT scan 5 years after surgery (2007). Signs of right upper and middle lobectomy with mediastinal shift to the same side. Lobulated and irregular lesion located in the right lower lobe (RLL) associated with bilateral micronodules. (B) Chest CT scan after first-line chemotherapy (April 2008) showed residual densification in the RLL and marked reduction in number and size of pulmonary metastases. (C) Chest CT scan before Erlotinib (July 2008) – Numerous bilateral pulmonary nodules predominantly in subpleural spaces and irregular thickening of interlobular septa. (D) Chest CT scan after 52 months of Erlotinib (November 2012) – Marked reduction in number and size of lung metastasis compared to July 2008 but stable in comparison to previous CT scan (not shown).

the remarkable response of this patient suggests that her metastatic tumor harbors an EGFR-TKI-sensitive mutation. In addition, there is some evidence that EGFR exon 19 deletion is associated with better responses to erlotinib and longer survival compared to exon 21 mutation [5,8] which suggests that exon 19 deletion might still be present in our patient.

According to a large international multicenter study (TRUST), unselected patients with advanced NSCLC who received erlotinib as second-line therapy had a median PFS and OS of 3.4 months and 8.6 months, respectively [17]. However, mutated Caucasian patients have a better outcome, especially females [5]. According to Rosell et al., median OS in women can achieve 29.0 months vs 18.0 months in men ($p = 0.05$) and regarding PFS, it is also significantly higher in this gender (16.0 vs 9.0 months; $p = 0.003$) [5]. Our patient is an excellent example concerning efficacy of erlotinib as a second-line therapy in an EGFR-positive Caucasian female, since she has already achieved a cumulative PFS of 52 months, which is extremely rare in literature.

One important issue raised by this case concerns acquired resistance to erlotinib. Recent data have shown that almost all patients with known EGFR mutations who initially respond to TKIs, subsequently become resistant due to emergence of mutations, such as T790M (in 50% of cases) and c-MET overexpression [15,16]. Generally, most tumors become resistance to TKIs within a median of 6–12 months [16] but this phenomenon has not occurred in our patient.

Our case strengthens the rationale for routine assessment of EGFR mutations as it determines the best therapy for patients with advanced NSCLC. Furthermore, it unequivocally shows that Erlotinib in an EGFR-positive patient with advanced NSCLC can provide an excellent quality of life and a remarkable control of the disease even as second-line treatment.

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