Curr Oncol, Vol. 19, pp. e222-226; doi: http://dx.doi.org/10.3747/co.19.908

CASE REPORT

Neoadjuvant erlotinib and surgical resection of a stage IIIA papillary adenocarcinoma of the lung with an L861Q activating *EGFR* mutation

M. Ong MD, K. Kwan MD,† S. Kamel–Reid PhD,‡ and M. Vincent MD**

ABSTRACT

The use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIS) is evolving, as is an understanding of predictive biomarkers for tumour response in non-small-cell lung cancer (NSCLC). In this report, we describe a case of rapidly progressing, borderline-resectable, clinical stage IIIA (micro) papillary adenocarcinoma in a 78-year-old woman who experienced a profound response to neoadjuvant erlotinib without short-term toxicity. On *EGFR* mutation testing, this patient had an uncommon activating point mutation at L861Q in exon 21. Her response permitted successful surgical resection with negative margins and avoidance of chemoradiation, which she was deemed too frail to tolerate. Our case addresses unique management issues such as preoperative testing for *EGFR* mutation, utility of histology in predicting *EGFR* mutations, and use of EGFR-TKIS pre- and postoperatively for potentially resectable NSCLC.

KEY WORDS

Papillary adenocarcinoma, *EGFR,* erlotinib, neoadjuvant

1. INTRODUCTION

Non-small-cell lung cancer (NSCLC) is well known to comprise a collection of biologically heterogeneous disease entities that exhibit variable sensitivity to cytotoxic and novel targeted therapies. Although chemotherapy, radiation, and surgery are often used in various combinations for the treatment of locally advanced NSCLC, tolerance of treatment remains a major concern, especially in frail elderly patients. The use and selection of targeted therapy in that setting remains poorly studied, but potentially better tolerated. Here, we report a case of locally advanced NSCLC in an elderly, deteriorating patient who was treated with neoadjuvant erlotinib and subsequent surgical resection.

2. CASE DESCRIPTION

A 78-year-old Caucasian woman presented in August 2009 with progressive nonproductive cough for 5 months and dyspnea and fatigue for 2 weeks. Her symptoms were unresponsive to clarithromycin, and chest radiography revealed a large, ill-defined right lower lung opacity. Past medical, family, and occupational history were not contributory; she had smoked 1 pack–year until age 22. Functionally, she was independent and had been swimming daily until 2 months earlier, but she was now dyspneic walking on level ground (Medical Research Council Dyspnea Index grade 3 [1]). Physical examination revealed diminished breath sounds at the right base. There was no digital clubbing. Blood count and chemistry were normal. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 1.

Staging computed tomography (CT) demonstrated a 7.4×5.6-cm mass in the right middle lobe and a 12-mm pre-carinal lymph node. Bronchoscopy was normal, but transbronchial biopsies (Figure 1) revealed numerous large malignant cells with glandular papillary structures and micropapillae positive for

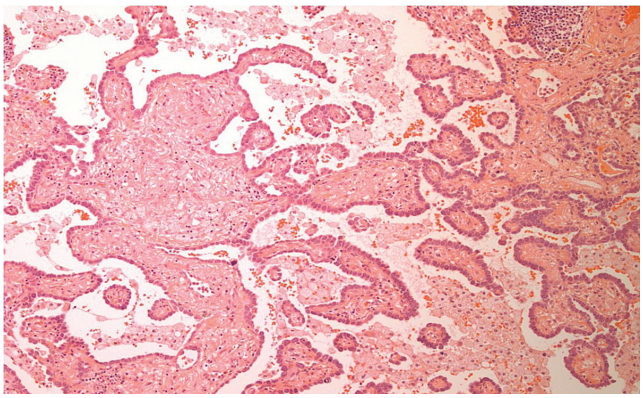

FIGURE 1 *Transbronchial biopsy of right-sided lung mass, revealing numerous large malignant cells with glandular structures and micropapillae, positive for cytokeratin 7 and thyroid transcription factor 1, but not for cytokeratin 20.*

cytokeratin 7 and thyroid transcription factor 1, and negative for cytokeratin 20, consistent with papillary adenocarcinoma of the lung.

The patient was assessed by Thoracic Surgery, and positron-emission tomography (PET)–CT showed enlargement of the mass to 10.5×8.2×6.7 cm in a 2-month interval, with extension to the lateral pleural surface [Figure 2(B)] and suspicion of a small right-sided malignant pleural effusion [standardized uptake value 2.7, Figure 2(A)]. The pre-carinal node was unchanged in size, and liver, adrenals, and brain were uninvolved. The mass was felt to be borderline resectable, and the predicted 1-second postoperative forced expiratory volume was 41% based on preoperative volume of 75%. A referral was made for concurrent chemoradiation.

Further assessment by medical and radiation oncology revealed worsening functional status (ECOG PS 2). The patient now had significant dyspnea on exertion and weight loss of 10 pounds over 2 months. Blood work revealed anemia (hemoglobin: 106 g/dL), thrombocytosis (423×10^9/L), elevated alkaline phosphatase [158 U/L (upper limit of normal: <126 U/L)], and elevated lactate dehydrogenase [432 U/L (upper limit of normal: <214 U/L)]. The patient was offered chemoradiotherapy, but alternative treatment was sought because of the declining PS and her preference to avoid chemotherapy or chemoradiation for fear of toxicity and worsened quality of life. Although her *EGFR* mutation status was not initially available, her papillary/micropapillary adenocarcinoma features, female sex, and light smoking history suggested a higher likelihood of *EGFR* activating mutation. At our centre, *EGFR* mutation testing was not routinely available at the time. After extensive discussion of her treatment options and a multidisciplinary review, the patient was started on erlotinib 150 mg daily in October 2009.

The patient was re-evaluated weekly while on erlotinib, and a rapid clinical and radiographic response was observed. Blood work normalized, including decline of lactate dehydrogenase to 147 U/L. Repeat CT imaging in mid-November showed diminishment of the mass to 2.9×4.5×3.9 cm and resolution of the pleural effusion [Figure 2(C)]. Side effects were mild: grade 1 diarrhea and xerosis of the skin.

Re-evaluation by Thoracic Surgery resulted in an uncomplicated right middle lobe lobectomy January 2010. Pathology revealed a 2.0×5.0×3.0 cm primary tumour, with no pleural involvement and negative margins. Fibrosis constituted 30% of the tumour volume. Lymph nodes at locations 4R and 11 were anthracotic only. The microscopy description revealed a mixed-subtype adenocarcinoma with a prominent papillary pattern and bronchioalveolar features without lymphovascular invasion. *EGFR* testing at an outside laboratory revealed no amplification by fluorescence *in-situ* hybridization, a point mutation (L861Q) in exon 21 of *EGFR* (Figure 3), and no *KRAS* mutation.

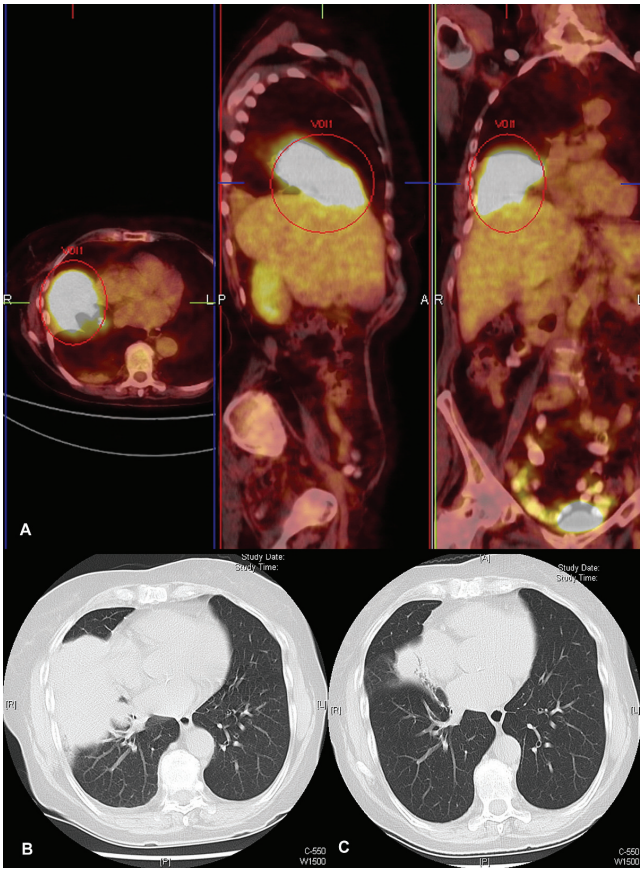

FIGURE 2 *(A) Fluorodeoxyglucose positron-emission tomography of the lungs demonstrates localized uptake in the right lower lobe. (B) Pre-erlotinib computed tomography for staging shows a 10.5×8.2×6.7-cm mass extending to the pleura. (C) Response after 3 months of erlotinib.*

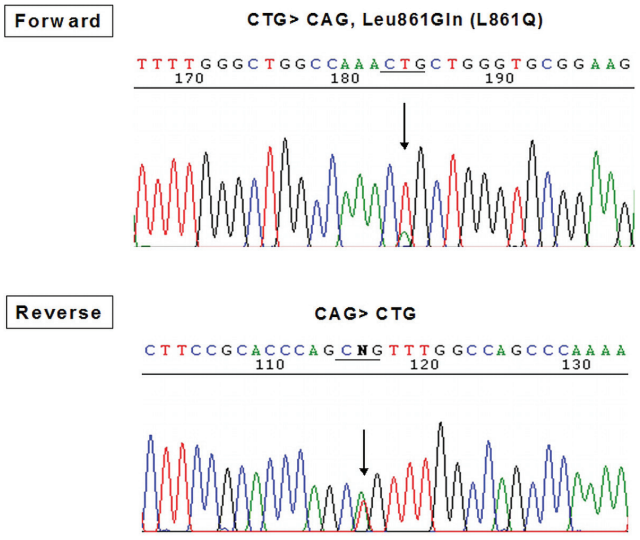

FIGURE 3 *EGFR mutational analysis on the resected lung mass (after neoadjuvant treatment with erlotinib) reveals an L861Q activating point mutation.*

The patient continued erlotinib 150 mg in the postoperative period. By March 2010, she had returned to an active lifestyle, swimming daily, with an ECOG PS of 0. Because of acneiform rash on the chest wall, two erlotinib dose reductions were instituted, and in May 2010, the patient was on erlotinib 50 mg daily. Unfortunately, in November 2010, she developed recurrent cough and fatigue. Imaging by CT revealed a locally recurrent right lower lobe mass and several right-sided pulmonary and pleural nodules. Erlotinib was discontinued. Thoracic Surgery felt that pneumonectomy was not indicated; the patient was treated with 3 cycles of doublet chemotherapy with carboplatin and vinorelbine.

Unfortunately, re-staging demonstrated further progression, and the patient's therapy was changed to second-line single-agent pemetrexed in February 2011. Initially, her lung nodules stabilized, but after 6 cycles (interspersed with palliative radiotherapy to the left 11th rib in May 2011), CT imaging in early July 2011 showed further disease progression. She was then switched to oral afatinib 40 mg daily through a special access program, achieving subjective improvement (relief of pain, cough, and dyspnea) and an objective partial response on that regimen, although requiring a dose reduction to 30 mg on alternating days because of grade 2 diarrhea coupled with a mild grade 1 rash. She currently remains on afatinib, with the diarrhea now completely controlled and no further evidence of disease progression, as of her most recent follow-up in April 2012.

3. DISCUSSION

This case represents a borderline resectable cT3N2M0 papillary adenocarcinoma of the lung, arising in an elderly woman with poor-PS who was a former light smoker. Her functional status did not favor concurrent chemoradiation, and chemotherapy alone was not preferred by the patient. Instead, 3 months of neoadjuvant erlotinib produced a promising response, that agent being justified based on the higher probability of *EGFR* mutation given her clinical and pathologic features [2,3], her baseline poor PS, and an approach of vigilantly monitoring her initial clinical response to treatment. Her tumour response allowed surgeons to perform a well-tolerated resection with negative margins. An eventual *EGFR* analysis was positive for a less-common L861Q activating point mutation in exon 21, and erlotinib was continued postoperatively for 10 months. Her recurrent tumour unfortunately highlights the limited understanding of the optimal management strategy for her situation.

Although not a preferred standard, neoadjuvant therapy of potentially resectable NSCLC is well described for conventional chemotherapy [4,5] and chemoradiation [6]. In some studies, age was an independent predictor of worse outcome [7]. Neoadjuvant use of EGFR-TKIs has been reported only anecdotally so far. One case reported from the Netherlands involved a 67-year-old never-smoker with PET-staged IIIA NSCLC with an *EGFR* exon 19 deletion [8]. That patient was treated with preoperative erlotinib, resulting in a rapid and complete pathologic response. Interestingly, PET-CT on treatment detected an early metabolic response. Two other cases were reported from Japan [9]. One patient with a cT2N2M1 tumour (adjacent lobe metastasis) had a substantial response to second-line gefitinib, with pT1N0M1 after resection and confirmation of an exon 19 deletion. A second patient with cT1N2M0 was shown to have an exon 21 L858R point mutation, with subsequent resection and demonstration of complete pathologic response.

Response to EGFR-TKI therapy is generally predicated on *EGFR* copy number or mutational status [10,11]. The use of EGFR-TKI without *EGFR* mutational testing in the first-line setting can be associated with harm, as demonstrated in IPASS (Iressa Pan-Asia Study) [11]. Patients in IPASS were selected to be a cohort enriched for *EGFR* mutation: Asian, nonsmokers or former light smokers, and adenocarcinoma histology. Those who were *EGFR* mutation-negative experienced worse progression-free survival (hazard ratio: 2.85; 95% confidence interval: 2.05 to 3.98; $p < 0.001$) if they received gefitinib rather than chemotherapy. Those data argue against the blind use of EGFR-TKIs, even after selection for clinical characteristics. However, in our patient's case, we judged her to be a poor candidate for chemotherapy because of age and frailty, and we monitored her closely for the possibility of harm on erlotinib.

The papillary adenocarcinoma histology in this patient favoured the possibility of *EGFR* mutation. Adenocarcinoma is most commonly of a mixed subtype (>90%), and papillary morphology represents a commonly dominant pattern. In one series of 100 patients with adenocarcinoma, the major histologic subtypes were papillary (33%), acinar (31%), solid with mucin (25%), bronchoalveolar (7%), and micropapillary (4%) [3]. Patients with major papillary morphology had a higher rate of *EGFR* mutations (55%) than did those with nonpapillary morphology (5%, $p < 0.001$), and micropapillary pattern was also correlated with *EGFR* mutation [3]. Micropapillary features are associated with aggressive disease and poor prognosis [12–14]. The lack of micropapillary features in the final resected pathology for our patient may reflect a change after neoadjuvant erlotinib treatment.

Although the exon 19 del and exon 21 L858R mutations represent the most common and well-described *EGFR* activating mutations, the exon 21 L861Q mutation occurs with relative frequency (5% in one series [15]) and is generally thought to confer sensitivity to EGFR-TKI therapy [16]; however, this mutation is infrequently reported in EGFR-TKI treated series [17–19]. Compared with exon 19 del or exon 21 L858R [20], L861Q may be less sensitive to EGFR-TKI.

Dose escalation of EGFR-TKI may be one strategy to overcome resistance [21]. Amplification or high polysomy of EGFR was not found in this patient's tumour. *EGFR* fluorescence *in-situ* hybridization positivity may occur independently of mutational status [22] and has been more associated with exon 19 del than with other mutations [23].

Erlotinib was continued post-resection in our patient, but the value of this approach is unknown. The NCIC Clinical Trials Group BR.19 study randomized 503 patients with resected stage IB–IIIA NSCLC to oral gefitinib 250 mg daily for 2 years or to placebo [24]. Overall survival trended in favor of placebo (hazard ratio: 1.23; $p = 0.136$), and patients with *EGFR* wild-type (hazard ratio: 1.21; $p = 0.301$) and *EGFR* mutation (hazard ratio: 1.58; $p = 0.16$) alike experienced nonsignificantly worse survival on gefitinib. That strongly counterintuitive result defies explanation, unless it relates to acceleration of drug-resistant forms of the disease. These data may or may not be applicable to situations in which the EGFR-TKI was started before surgery, but they do argue that EGFR-TKI may not have to be maintained postoperatively. On the other hand, if our patient's tumour had not been resected, there would be no question of continuing the erlotinib until progression or intolerance.

4. CONCLUSIONS

With this case, we have added to the meager world literature on neoadjuvant administration of the EGFR-TKIs. Without short-term toxicity, erlotinib provided a rapid and profound response in a (micro)papillary adenocarcinoma of the lung, which permitted a safe and ostensibly complete surgical resection. In this frail and declining patient, we provided effective initial palliation rather than the more dubious option of chemoradiation. However, the duration of response was short, perhaps reflective of the aggressive micropapillary histology. Learning points include these:

- Response to erlotinib can be rapid in an *EGFR*-mutated NSCLC tumour, with improvement in surgical resectability.
- *EGFR* mutations with (micro)papillary morphology are frequent, but not frequent enough to obviate the need for *EGFR* testing.
- The effectiveness of neoadjuvant erlotinib is still unknown and the subject of ongoing clinical trials.
- The role and effectiveness of EGFR-TKIs post resection remain controversial.

5. CONFLICT OF INTEREST DISCLOSURES

MO has no financial conflict of interest to disclose. MV has received honoraria for speaking engagements and advisory boards, and research funding from Hoffmann–La Roche Canada Inc.

6. REFERENCES

1. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J* 1959;2:257–66.
2. Ninomiya H, Hiramatsu M, Inamura K, *et al.* Correlation between morphology and *EGFR* mutations in lung adenocarcinomas. Significance of the micropapillary pattern and the hobnail cell type. *Lung Cancer* 2009;63:235–40.
3. Motoi N, Szoke J, Riely GJ, *et al.* Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, *EGFR* mutations and gene expression analysis. *Am J Surg Pathol* 2008;32:810–27.
4. van Meerbeeck JP, Kramer GW, Van Schil PE, *et al.* on behalf of the European Organisation for Research and Treatment of Cancer–Lung Cancer Group. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–50.
5. Felip E, Rosell R, Massuti B, *et al.* The NATCH trial: observations on the neoadjuvant arm [abstract 7578]. *J Clin Oncol* 2007;25:. [Available online at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=32833; cited April 6, 2012]
6. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379–86.
7. Paul S, Mirza F, Port JL, *et al.* Survival of patients with clinical stage IIIA non-small cell lung cancer after induction therapy: age, mediastinal downstaging, and extent of pulmonary resection as independent predictors. *J Thorac Cardiovasc Surg* 2011;141:48–58.
8. Kappers I, Klomp HM, Burgers JA, Van Zandwijk N, Haas RL, van Pel R. Neoadjuvant (induction) erlotinib response in stage IIIA non-small-cell lung cancer. *J Clin Oncol* 2008;26:4205–7.
9. Takamochi K, Suzuki K, Sugimura H, *et al.* Surgical resection after gefitinib treatment in patients with lung adenocarcinoma harboring epidermal growth factor receptor gene mutation. *Lung Cancer* 2007;58:149–55.
10. Paez JG, Jänne PA, Lee JC, *et al. EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–500.
11. Mok TS, Wu YL, Thongprasert S, *et al.* Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
12. Makimoto Y, Nabeshima K, Iwasaki H, *et al.* Micropapillary pattern: a distinct pathological marker to subclassify tumours with a significantly poor prognosis within small peripheral lung adenocarcinoma (≤20 mm) with mixed bronchioloalveolar and invasive subtypes (Noguchi's type C tumours). *Histopathology* 2005;46:677–84.
13. Miyoshi T, Satoh Y, Okumura S, *et al.* Early-stage lung adenocarcinomas with a micropapillary pattern, a distinct pathologic marker for a significantly poor prognosis. *Am J Surg Pathol* 2003;27:101–9.

14. Nassar H. Carcinomas with micropapillary morphology: clinical significance and current concepts. *Adv Anat Pathol* 2004;11:297–303.
15. Tam IY, Chung LP, Suen WS, *et al.* Distinct epidermal growth factor receptor and *KRAS* mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* 2006;12:1647–53.
16. Chen YR, Fu YN, Lin CH, *et al.* Distinctive activation patterns in constitutively active and gefitinib-sensitive *EGFR* mutants. *Oncogene* 2006;25:1205–15.
17. Kim DW, Lee SH, Lee JS, *et al.* A multicenter phase II study to evaluate the efficacy and safety of gefitinib as first-line treatment for Korean patients with advanced pulmonary adenocarcinoma harboring *EGFR* mutations. *Lung Cancer* 2011;71:65–9.
18. Costa DB, Nguyen KS, Cho BC, *et al.* Effects of erlotinib in *EGFR* mutated non-small cell lung cancers with resistance to gefitinib. *Clin Cancer Res* 2008;14:7060–7.
19. Sequist LV, Martins RG, Spigel D, *et al.* First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic *EGFR* mutations. *J Clin Oncol* 2008;26:2442–9.
20. Kancha RK, Peschel C, Duyster J. The epidermal growth factor receptor-L861Q mutation increases kinase activity without leading to enhanced sensitivity toward epidermal growth factor receptor kinase inhibitors. *J Thorac Oncol* 2011;6:387–92.
21. Hirano S, Sano K, Morii S, *et al.* A case of lung adenocarcinoma successfully treated with dose-reescalated gefitinib after resistance was acquired [Japanese]. *Gan To Kagaku Ryoho* 2009;36:1333–6.
22. Schneider CP, Heigener D, Schott-von-Römer K, *et al.* Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer: an analysis of patients from German centers in the TRUST study. *J Thorac Oncol* 2008;3:1446–53.
23. Sholl LM, Yeap BY, Iafrate AJ, *et al.* Lung adenocarcinoma with *EGFR* amplification has distinct clinicopathologic and molecular features in never-smokers. *Cancer Res* 2009;69:8341–8.
24. Goss GD, Lorimer I, Tsao MS, *et al.* A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19 [abstract LBA7005]. *J Clin Oncol* 2010;28:. [Available online at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=48314; cited: April 6, 2012]

Correspondence to: Mark D. Vincent, London Health Sciences Centre, London, Ontario N6A 4L6.
E-mail: Mark.Vincent@lhsc.on.ca

* Department of Oncology, London Health Sciences Centre, London, ON.
† Department of Pathology, London Health Sciences Centre, London, ON.
‡ Ontario Cancer Institute, Princess Margaret Hospital, Toronto, ON.