Cancer Treatment and Research Communications 11 (2017) 10–16

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Challenging the Paradigm: EGFR wild-type benefit from an EGFR inhibitor in NSCLC

Barb Melosky[a,*], Brandon S. Sheffield[b], Mei-Hua Tsou[c], S. Eric Gagne[b], Diana N. Ionescu (Naus)[d,e,f,g], James Chih-Hsin Yang[h]

[a] British Columbia Cancer Agency, Vancouver Centre, 600- 10th Ave W, Vancouver, BC, Canada V5Z 4E6
[b] Contextual Genomics Inc. 204-2389 Health Sciences Mall Vancouver, BC Canada
[c] Dept. Pathology & Laboratory Medicine, Koo Foundation Sun Yat-Sen Cancer Center, 125, Lide Rd, Beitou Dist, Taipei, Taiwan
[d] AP Residency Program Director, UBC, Department of Pathology, BC Cancer Agency, Vancouver, BC, Canada
[e] Clinical Professor, UBC, Vancouver, BC, Canada
[f] Medical Director Clinical Trials, BCCA Laboratories, Vancouver, BC, Canada
[g] Consultant Pathologist, UBC, Department of Pathology, BC Cancer Agency, Vancouver, BC, Canada
[h] Graduate Institute of Oncology and Department of Oncology, National Taiwan University and National Taiwan University Hospital, Taiwan

ARTICLE INFO

Keywords:
Non-small cell lung cancer
NSCLC
EGFR mutation
Erlotinib
Gefitinib
Afatinib
Tyrosine kinase inhibitor
TKI, Case study

ABSTRACT

Erlotinib and gefitinib are first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). Afatinib is a second generation pan-Her EGFR TKI. All three TKIs have demonstrated superiority to chemotherapy in the first line setting in patients harboring an *EGFR* mutation in the EURTAC [1], IPASS [2], LUX-LUNG 3 [3] and LUX-LUNG 6 [4] trials.

This article describes the case of a patient treated at a Cancer Centre in Taiwan and at the British Columbia Cancer Agency in Canada. This patient experienced a remarkable response to a number of different systemic treatments. Despite not having a detectable *EGFR* mutation, he had a positive and prolonged response to all three EGFR TKIs. This case challenges current treatment paradigms for the treatment of a NSCLC patient whose tumour does not have an activating *EGFR* mutation.

1. Introduction

This article describes the case of a patient treated at a Cancer Centre in Taiwan and at the British Columbia Cancer Agency in Canada. This patient experienced a remarkable response to a number of different systemic treatments. Despite not having a detectable *EGFR* mutation, he had a positive and prolonged response to all three EGFR TKIs.

1.1. Asymptomatic at initial diagnosis

Mr.X[1] was an Asian non-smoker and former engineer whose lung cancer was first diagnosed in Taiwan in December 2007, at the age of 66. He had no history of carcinogen or second hand smoke exposure or asbestosis, and had experienced a dry cough in the two years prior to his diagnosis. A chest x-ray conducted as part of a routine physical exam revealed an abnormality in his right upper lung. A PET/CT scan revealed a right upper lung mass and hilar/mediastinal adenopathy. Hypermetabolic lesions were seen in the right hilar, subcarinal, pericardial and right paratracheal lymph nodes consistent with malignancy.

In January 2008, he underwent a right upper lung wedge resection and paratracheal and mediastinal lymph node dissection in Taiwan. All resections were positive for adenocarcinoma and he was staged as stage IIIA non-small cell lung cancer (NSCLC).

1.2. First line treatment in Taiwan

Mr.X started the first of a series of different treatments for his lung cancer. Adjuvant treatment included six cycles of carboplatin/vinorelbine from February to June 2008. Unfortunately, during the last cycle

Abbreviations: BCCA, British Columbia Cancer Agency; CTNNB1, Catenin Beta 1; EGFR, Epidermal Growth Factor Receptor; FISH, Fluorescent *in situ* hybridization; HER 2, Human Epidermal Growth Factor Receptor 2; M+, Mutation-positive; NCI, National Cancer Institute; NSCLC, Non-small cell lung cancer; PFS, Progression Free Survival; TKI, Tyrosine Kinase Inhibitor; WT, Wild-type

* Corresponding author.
E-mail addresses: bmelosky@bccancer.bc.ca (B. Melosky), bsheffield@contextualgenomics.com (B.S. Sheffield), MHTSOU@kfsyscc.org (M.-H. Tsou), egagne@contextualgenomics.com (S.E. Gagne), dionescu@bccancer.bc.ca (D.N. Ionescu (Naus)), chihyang@ntu.edu.tw (J.C.-H. Yang).

[1] Not real name.

http://dx.doi.org/10.1016/j.ctarc.2017.02.005
Received 25 November 2015; Received in revised form 31 October 2016; Accepted 28 February 2017

of his adjuvant treatment, he demonstrated progressive lymphangitic disease in keeping with stage IV NSCLC. We assumed that metastatic disease was present earlier, and so the adjuvant therapy is considered first line metastatic treatment.

1.3. Second line gefitinib

One month later, Mr. X was symptomatic with shortness of breath and his performance status dropped to 2. A CT revealed progressive hilar adenopathy, mediastinal, left supraclavicular lymph nodes, and multiple pulmonary nodules. In July 2008, he started treatment with second line gefitinib at 250 mg per day.

1.4. Presentation and examination at BCCA

Mr.X returned to Canada in September 2008. After two months of gefitinib, he was clinically responding with improvements to his cough and chest pain. He appeared well and in no acute distress and his performance status was 1. During a consultation at the British Columbia Cancer Agency (BCCA), his physical exam was normal and no lymphadenopathy was palpable. The results of his respiratory system examination were unremarkable.

1.5. Prognosis: one year survival

During the consultation, a significant amount of time was spent discussing his prognosis. As a patient with stage IV lung adenocarcinoma who had progressed quickly on adjuvant therapy, his disease was considered to be aggressive. His prognosis was estimated to be approximately one year and his five-year survival was estimated to be between 5 and 10%. This consultation was conducted before the implication of having an *EGFR* mutation was known and the patient left the consultation with the expectation that he had one year to live.

1.6. Switched to second line erlotinib

At the time of this consult the patient was still taking gefitinib, but was switched to erlotinib, at 150 mg per day, as this was the EGFR TKI approved in Canada in the second line setting. A CT scan done in October 2008, showed that the pleural-based mass along the major fissure of the right lung measured 3.5 by 1.5 cm. Carcinomatosis and nodules were observed in his left upper lung (Fig. 1A). By January 2009, after four months of erlotinib treatment, the CT scan showed a response (Fig. 1B). The carcinomatosis was resolved and the mass was now 3.0 by 1.0 cm. Mr.X continued to benefit from erlotinib treatment for another year, thus was on first generation TKIs (gefitinib + erlotinib) for a total of 15 months.

In February 2010, Mr.X started to experience increasing shortness of breath and chest pain. His CT scans showed bilateral pleural effusions and a pericardial effusion (Fig. 2A and B). He was in cardiac tamponade and was urgently admitted to the hospital. His pericardial fluid was drained and a PleurX catheter was placed in his right chest cavity.

Pathological analysis of the pericardial fluid confirmed adenocarcinoma. The tumor cells exhibited positive immunohistochemistry staining for MOC31, EP4, monoclonal CEA, and TTFI, supporting the primary lung origin of this neoplasm and epithelial differentiation. The erlotinib was discontinued.

1.7. Third line treatment with Pemetrexed

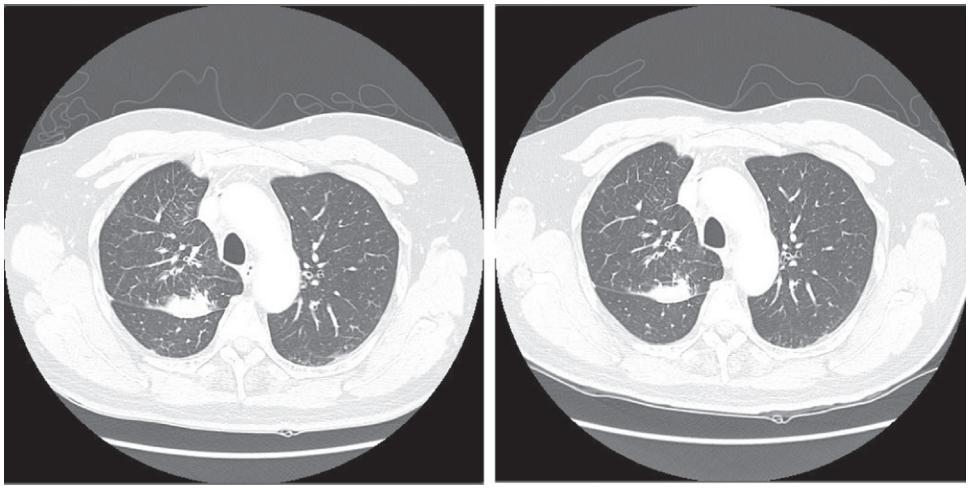
By mid-March, Mr.X was still in the hospital as he was extremely ill. He was switched to third line pemetrexed and after one dose, he was discharged. After four doses of pemetrexed, in June 2010, he was re-admitted to the hospital with a fever, sore throat, right earache and with his blood culture positive for group A streptococcus and his pemetrexed was interrupted. CT scans during his July 2010 admission showed that the mass in the right lung was reduced to 2.5 by 1.2 cm, the pericardial effusion resolved (Fig. 3A and B). He resumed treatment with pemetrexed for an additional four doses.

In December 2010, he was clinically progressing with an increasing shortness of breath. His CT showed an increased growth in the mass in his right lung, 3.3 by 1.6 cm, (Fig. 4A) and there was increased bibasilar consolidation and evidence of lymphocytic carcinomatosis. There was a new loculated pericardial effusion and enlargement of left pleural effusion (Fig. 4B).

Mr.X underwent screening for the National Cancer Institute of Canada CTG BR.26 trial, a phase III randomized, double blind, placebo controlled trial of a second generation pan-Her inhibitor dacomitinib versus placebo in patients with advanced/metastatic NSCLC. The BR 26 trial required an ejection fraction of $\geq$ 50%; as his cardiology consultation in November 2010 revealed that his echocardiogram was only 45%, he was ineligible for the trial. Increasingly symptomatic, Mr.X's performance status fell to 2–3.

1.8. Afatinib in the fourth line

At the end of January 2011, Mr. X started on afatinib at a dose of 40 mg per day, through the Health Canada Special Access Program.



A. October 2008 CT scan. Pleural-based mass on right lung fissure, 3.5 x 1.5 cm.

B. January 2009 CT scan. Mass is 3.5 x 1.0 cm and carcinomatosis is resolved.

Fig. 1. A. October 2008 CT scan. Pleural-based mass on right lung fissure, 3.5 × 1.5 cm. **B**. January 2009 CT scan. Mass is 3.5 × 1.0 cm and carcinomatosis is resolved.