

Long Term Survivor with Erlotinib in Metastatic Lung Cancer-Squamous Cell Carcinoma Subtype

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ABSTRACT: Currently, data that supports the clinical benefit of agents targeting the epidermal growth factor receptor (EGFR) in the therapy of squamous cell carcinoma (SCC) histologic version of the lung cancer (LC) is insufficient. In the following report we present the case of a patient treated with erlotinib for SCC NSCLC. At the time of initiation, there were no available guidelines recommendations regarding the EGFR status in for initiation of EGFR tyrosine kinase inhibitors (TKIs) therapy for NSCLC, thus the sample was never tested for the EGFR mutational status. Not widely used in the treatment of SCC, EGFR-TKIs remain a valid therapeutic option in selected groups of patients.

KEYWORDS: Non-small cell lung cancer, TKI, EGFR, EGFR-TKIs, erlotinib, targeted therapy.

Introduction

LC has been regarded as the number two cause of death worldwide and in the United States of America (USA) LC is responsible for the majority of cancer related deaths both in males and females [1].

According to the World Health Organization (WHO), in the European Union (EU) about 20 percent of total deaths are attributed to cancer, LC being the most prevalent and the leading cause of death amongst cancer patients [1].

NSCLC represents 80% of all LC and SCC subtype accounts for about 25% of NSCLC. The vast majority of patients with NSCLC are diagnosed in an advanced or metastatic stage, with survival being 6 months from the time of diagnosis till death [2].

Up until a few years ago, chemotherapy was the only viable treatment option for patients with SCC LC. The advent of targeted therapy some twenty years ago has paved the road for very promising therapeutic options for an ever-growing number of cancers. Particularly, in lung cancer, the EGFR-TKIs are currently being used to treat NSCLC that harbor EGFR mutations as a first line setting in advanced and metastatic disease [3].

EGFR-TKIs have presented a clear improvement in the treatment of NSCLC in terms of progression free survival (PFS) and an improvement in quality of life (QoL) when compared to chemotherapy [4,5].

Unfortunately, while EGFR-TKIs have demonstrated a clear effect in a subgroup of adenocarcinoma patients harboring a specific mutation, no clear benefit has been observed for those with the SCC subtype. However, a few case reports have noted a benefit for patients with the SCC subtype after receiving EGFR TKIs [6].

According to the latest guidelines, EGFR mutation status testing is an integral part of standard care in LC. The American Association for Clinical Oncology (ASCO), The European Association for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) publish guidelines regarding EGFR status testing in patients with SCC LC [3].

According to ASCO, all NSCLC cases should be included in the testing for EGFR mutational status, if they are eligible for first-line therapy with an EGFR-TKI [7].

In Europe, the ESMO has reached a consensus which recommends that all patients who are never/former light smokers and those with non squamous cell should be tested for the EGFR mutation [8].

The NCCN guidelines strongly recommend that all never smokers, patients with small biopsy specimens, or those with mixed histology should have the EGFR mutation investigated via immunohistochemistry if they have been previously diagnosed with the SCC subtype [3].

As a conclusion, ASCO encourages EGFR mutation testing for all SCC cases when the patients are candidates for EGFR-TKIs therapy while ESMO/NCCN guidelines recommend

EGFR testing for several clearly defined situations [3,7,8].

More interestingly, in the past decade, a number of studies have highlighted that the incidence of EGFR mutations in SCC samples was between 3.9%-17.2%, which is higher than expected [9-11].

Erlotinib is a first generation TKI used for the treatment of locally advanced or metastatic NSCLC and for therapy of patients diagnosed with pancreatic cancer in locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine [12,13].

It was approved following the results of phase III BR.21 study, since 2004 by the Food and Drug Administration (FDA) in the second and third line setting for locally advanced and metastatic NSCLC treatment regardless of EGFR mutational status [14].

Since 2004, multiple studies have shown that erlotinib has a higher clinical benefit in the subpopulation of patients with NSCLC that had non-SCC histology, who were females and never smoked.

Case Study

In this study we present the case of a 67 year old man, diagnosed 11 years ago (July 2009) with stage IV NSCLC, former heavy smoker, with a SCC tumor histology who was treated for nine years with erlotinib in the second line setting, following relapse after first line chemotherapy with a platinum doublet. The patient signed the informed consent granting access to the information presented in this article strictly for scientific purposes only.

The patient was first admitted in the „Bagdasar Arseni” Emergency Hospital in Bucharest, Romania in July 2009 for headaches, dizziness and aphasia. He lived in an urban home and had a medical history of asthma and chronic obstructive broncho pneumopathy.

The neurological exam performed at admittance discovered that the patient was unable to walk or stand up, presented a hemiparesis of the right upper limb, right nasolabial fold flattening and aphasia.

The computer tomography (CT) (Figure 1) and magnetic resonance imaging (MRI) brain scans showed a left parietal brain lesion about 10mm in its greatest diameter.

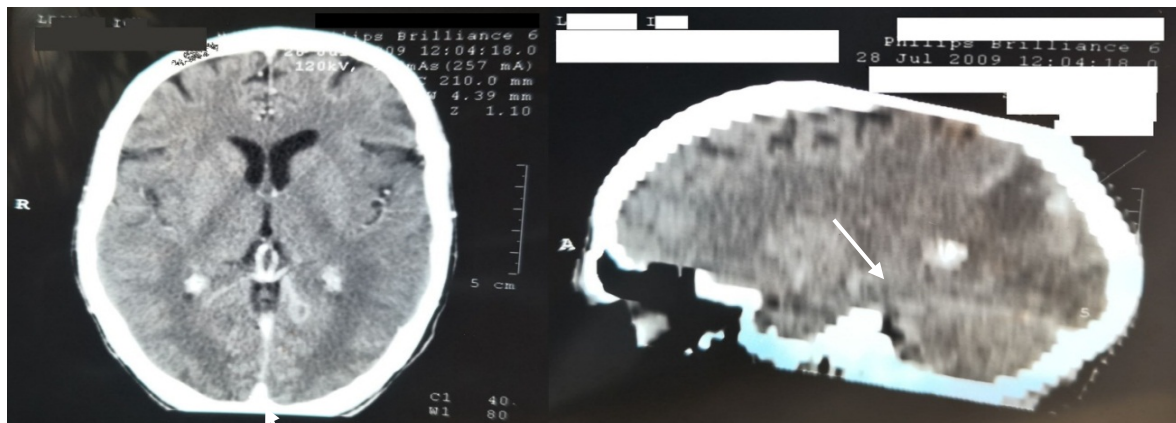


Figure 1. Left parietal brain lesion, (lateral and transversal view), 2009.

Chest X-ray shows a tumor in the right inferior lung lobe. Abdominal ultrasound shows no pathological finds. Chest CT scan confirmed the tumour in the right inferior lung lobe. Cardiology and ophthalmology exams showed no abnormalities.

The initial blood count, liver and renal functions showed modified values in fibrinogen (FiB): 538mg% and Erythrocyte sedimentation rate (ESR): 40mm/hour.

Bronchoscopy was negative. The forced vital capacity (FVC), FEV (forced expiration ventilation) and diffusing capacity of carbon

monoxide (DLCO) showed a mild respiratory restrictive obstruction.

Five days later the patient receives gamma knife radiosurgery for the brain lesion, a total of 0.9Gy over a tumoral volume of 1,6 cubic centimeters tissue mass being delivered. He then undergoes surgery and the right inferior lung lobe is removed together with mediastinal lymph node dissection.

The histopathological examination of the sample presented the following results: A 13/7/5cm lobectomy piece with a 6cm diameter tumor with pleural invasion and massive

necrosis. The microscopic evaluation described a poorly differentiated epidermoid squamous carcinoma with clear invasion of the visceral pleura. No lymph node invasion was detected. The post-intervention stage was pT2pN0M1. No immunohistochemistry was performed at the time.

Following the multidisciplinary team (MDT) evaluation the diagnosis of stage IV (M1BRA) right inferior lobe NSCLC is established.

On the 21st of November 2009 the patient begins first line chemotherapy with cisplatin and gemcitabine administered at a 21 days interval for a total of nine cycles, until 24th of June 2010.

The chest and abdominal CT scan evaluation performed six months after chemotherapy, shows pretracheal and laterotracheal lymph node enlargement (under 10mm largest diameter) and

blood tests show an elevated gamma glutamyl transferase of 69.6U/L. We considered progressive disease after first line chemotherapy and started second line treatment with EGFR TKI-erlotinib. This decision was taken based on clinical experience as there were no clear guideline indications for TKIs therapy in NSCLC, based on the immunohistochemical analysis of driver mutations.

In December 2010 the patient started second line therapy with erlotinib 150mg daily continued to this day.

CT scans of the chest (Figure 2a) and brain MRI (Figure 3), abdominal US and blood tests, performed at a 6 month interval show no evidence of progressive disease. There is a residual left parietal lesion described in every CT scan since gamma knife surgery and post-surgery right lobe scarring (Figure 2b).

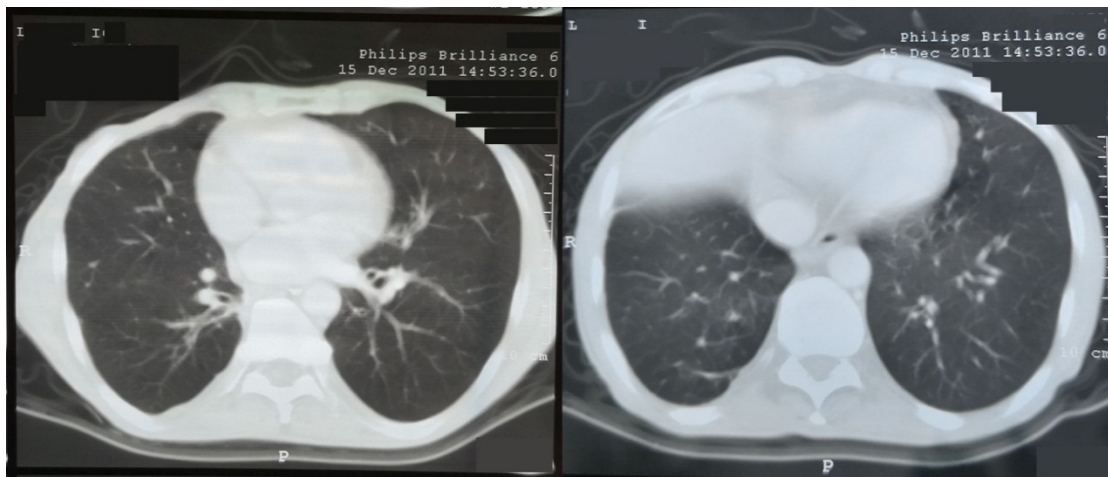


Figure 2. Thorax - transversal view, 2011 with no signs of local disease (a) and residual right lobe scarring (b).



Figure 3. Brain section transversal view, left parietal lesion post Gamma Knife treatment, 2014.

Discussion

NSCLC that has spread to other parts of the body is often hard to treat. The 5-year survival rate for stage IVA NSCLC is about 10%, and for stage IVB the 5-year survival rate is less than 1% [15].

SCC is responsible for almost a quarter of all lung cancer cases, second only to adenocarcinomas.

It has several particular traits which make its diagnosis and treatment different from other LC types.

First and foremost, its' usually appears from cells belonging to the central respiratory airways, making it the most likely subtype to cause an obstructive respiratory syndrome [16].

SCC is strongly linked to a personal history of long-term tobacco consumption which contains a large number of DNA-altering toxins.

As such, it was strongly expected that SCC would present a plethora of mutations and other types of genetic alterations with targeting potential.

Paradoxically, no mainstay driver mutation has been identified in the case of SCC. EGFR, which has been strongly linked to the development and evolution of adenocarcinomas has presented a meager influence in the genesis of SCC.

However, there are several clinical trials which suggest that anti-EGFR treatment might be a valuable option for the treatment of SSC.

A multicenter phase III trial from 23 countries analyzed the effect of Afatinib vs. Erlotinib for second line treatment of stage IIIB and IV non-resectable SCC.

The study showed markedly improved OS and PFS for the patients who received Afatinib underscoring that even though the earlier generations of anti-EGFR TKIs presented favorable results in only a select number of cases the newer molecules might play a larger role [17].

Another study showed that the anti-EGF antibody necitumumab alongside gemcitabine was superior to the standard cisplatin-gemcitabine doublet in the treatment of EGFR-expressing SCC patients, in terms of both OS and PFS.

The safety profile for both gemcitabine and necitumumab and necitumumab as maintenance therapy was more favorable when compared to the combined chemotherapy regimen which is known to have multiple adverse effects [18].

In our case, when the targeted treatment was initiated, there were no guidelines for EGFR mutational status testing and EGFR-TKIs could be prescribed as part of the treatment panel strategy of NSCLC regardless of histopathological type or EGFR.

Our patient benefited from erlotinib as a second line option following progression after first line platinum doublet.

It is worth mentioning that in this case we did not have an accurate description on the number of lymph nodes resected at the time of surgery.

The number of lymph nodes were not assessed prior to surgery through Endoscopic Ultrasound (EUS) or Endobronchial Ultrasound (EBUS).

Biopsy from the brain lesion was not obtained because the MDT panel decided the risk-benefit ratio was unacceptable for the patient at that moment.

In this case there is a disease free interval of 97 months, last CT scan, performed in May 2019 showing the same left parietal residual lesion as before and right lung post-surgery scarring.

Conclusion

The presented case, underlines that even in SCC of the lung where ESMO and NCCN guidelines are specific with EGFR testing, EGFR-TKIs may play a role in the treatment of certain patients and EGFR mutational status should be part of the initial panel of explorations for every NSCLC patient diagnosed.

List of abbreviations

Epidermal growth factor receptor-EGFR; Tyrosine Kinase Inhibitor-TKI; LC-Lung Cancer; NSCLC-Non-small cell lung cancer; Squamous Cell Carcinoma-SCC; American Association for Clinical Oncology-ASCO; European Association for Medical Oncology-ESMO; National Comprehensive Cancer Network-NCCN; Food and Drug Administration FDA; progression free survival-PFS; quality of life-QoL; United States of America-USA; World Health Organization-WHO; computer tomography-CT; magnetic resonance imaging-MRI; multidisciplinary team-MDT; forced vital capacity-FVC, FEV-forced expiration ventilation; diffusing capacity of carbon monoxide-DLCO; Endoscopic Ultrasound (EUS)

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Bogdan-Ionel Vatu and Cristian Tuta share equal contributions to this work.

Conflict of interests

None to declare.

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