Significant benefits of osimertinib in treating acquired resistance to first-generation EGFR-TKIs in lung squamous cell cancer: A case report

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Abstract

BACKGROUND
Lung squamous cell cancer (LSCC) rarely harbors epidermal growth factor receptor (EGFR) mutations, even much rarer for acquired T790M mutation. Although clinical trials of AURA series illustrated that non-small cell lung cancer (NSCLC) with EGFR T790M mutation can benefit from osimertinib, only five LSCC patients were enrolled in total; moreover, the efficacy for LSCC was not shown in the results. Therefore, the response of LSCC to osimertinib is still unclear to date.

CASE SUMMARY
We report an LSCC case with T790M-related acquired resistance after treatments with first-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and benefited from osimertinib significantly. A 63-year-old Chinese man was diagnosed with stage IV (cT2N2M1b) LSCC harboring an EGFR exon 19-deletion mutation. Following disease progression after gefitinib and multi-line chemotherapy, re-biopsy was conducted. Molecular testing of EGFR by amplification refractory mutation system-polymerase chain reaction detected the exon 19-deletion without T790M mutation. Therefore, the patient was given erlotinib, but progression developed only 3 mo later. Then the frozen re-biopsy tissue was
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INTRODUCTION

The oncogenic driver profile of lung squamous cell lung cancer (LSCC) is significantly different from that of lung adenocarcinoma\(^1\). Epidermal growth factor receptor (EGFR) is the most important driver gene in lung adenocarcinoma; therefore, LSCC rarely harbours EGFR mutations\(^2\)\(^-\)\(^4\).

Although lung adenocarcinoma can benefit from EGFR-tyrosine kinase inhibitors (TKIs) and the acquired resistance mechanism has been widely researched\(^5\), the data for LSCC are very limited due to the rare incidence of EGFR-positive LSCC. We previously performed a multicentre retrospective study of EGFR-positive LSCC patients treated with EGFR-TKI\(^5\), which showed that the progression-free survival (PFS) for LSCC is only 5.1 mo\(^6\), significantly inferior to lung adenocarcinoma, which is about 9.7 to 13.1 mo\(^7\)\(^-\)\(^9\). This indicates that the EGFR signalling pathway in LSCC may not be identical to that in adenocarcinoma.

Osimertinib, an oral, potent, irreversible EGFR-TKI, has been reported to be highly effective in patients with EGFR T790M mutation-positive non-small-cell lung cancer (NSCLC) in previous three clinical trials of the AURA series. Although 882 NSCLC patients were enrolled in the three clinical trials, only five LSCC patients were included (3 from AURA, 2 from AURA2, and 0 from AURA3); moreover, the efficacy of osimertinib for LSCC was not shown in the results\(^10\)\(^-\)\(^12\). T790M-positive LSCC is rarely reported. Only 14 additional cases were reported previously in addition to the cases in the AURA series clinical trials; however, none of these patients were treated with osimertinib\(^13\)\(^-\)\(^20\). Although one patient with a T790M mutation was administered with another third-generation EGFR-TKI, rociletinib, this was an LSCC transformation from adenocarcinoma, rather than acquired resistance to first-generation TKIs\(^20\). The response of LSCC to osimertinib is still unclear to date. More
clinical evidence is needed for the management of LSCC with T790M after treatment with first-generation EGFR-TKIs.

Here, we report an LSCC patient with T790M-related acquired drug resistance after treatments with first-generation EGFR-TKIs who benefited from the third-generation EGFR-TKI osimertinib.

CASE PRESENTATION

Chief complaints
A 62-year-old male patient was initially admitted to our hospital due to cough and sputum for one month and hemoptysis for ten days.

History of present illness
One month ago, the patient developed symptoms of cough, expectorated white phlegm, but did not take any medicine. Then, he began suffering hemoptysis then days ago.

History of past illness
Unremarkable.

Personal and family history
The patient had a long-term history of smoking for about 40 years (10 cigarettes per day) without personal or family history of other diseases.

Physical examination upon admission
At admission, he was conscious with a regular heart rate of 75 bpm and a blood pressure of 128/75 mmHg. He had lost 4 kg weight in the past two months. Left lower lung breath sounds weakened. The other physical examinations were normal.

Laboratory examinations
Results of laboratory routine examinations including complete blood count, fecal occult blood, blood biochemistry, and urine were within normal limits. But his carcinoembryonic antigen was 6.93 ng/mL (reference, <3.4 ng/mL) and cytokeratin 19 fragment antigen 21-1 was 14.63 ng/mL (reference, <3.0 ng/mL).

Imaging examinations
Computed tomography of the chest revealed an occupying lesion in the inferior lobe of the left lung (Figure 1A) with hilar and mediastinal lymphadenectomy (Figure 1B). Magnetic resonance imaging showed abnormal long T1 and T2 signals at the right femoral neck and ischium and radionuclide bone imaging revealed increased bone uptake on TC-99m (Figure 1C-E).

FINAL DIAGNOSIS

Histological examination of a transbronchial lung biopsy and a cytological examination of the bronchus and sputum confirmed LSCC, without adenosquamous carcinoma or mixture of other components. The final diagnosis was stage IV (cT2N2M1b) LSCC. We also tested for EGFR mutations by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR; AmoyDx, Xiamen, China) using a small biopsy specimen. We found that this patient had an EGFR exon 19 deletion mutation.

TREATMENT

Systemic treatments were subsequently administered (Figure 2). The patient began initial gefitinib 250 mg per day from November 2013 and had a partial response until June 2014, when CT scans showed disease progression in the left lung and new metastases in the rib and abdominal lymph nodes. He subsequently stopped gefitinib and started combination chemotherapy with gemcitabine and cisplatin for two cycles. Unfortunately, he again developed disease progression in the lung and T11 costotransverse joint. Then, second-line docetaxel and cisplatin were administered for two cycles. After treatment, he complained of headaches, and brain MRI showed disease progression with multiple new lesions in the left cerebellum. Subsequently, he was treated with whole brain radiotherapy (WBRT, 37.5 Gy/2.5 Gy/15 f) and
Figure 1  Baseline imaging examinations. Primary cancer in the inferior lobe of the left lung (A, arrow) with metastases to the hilar and mediastinal lymph nodes (B, arrow) and multiple bones (C-E, arrows).

chemotherapy with vinorelbine alone (20 mg/m² intravenously days 1, 8, 15, once every 4 wk). However, chemotherapy scheduled on day 15 was discontinued due to severe bone marrow suppression.

The patient underwent re-biopsy of the left lung mass through CT-guided percutaneous puncture, and two specimens were obtained. One specimen was formalin-fixed and paraffin-embedded for pathological and gene alteration tests, and the other was stored in liquid nitrogen. Pathological testing showed identical LSCC (Figure 3), and molecular testing of EGFR by ARMS-PCR quantified the exon 19 deletion without the T790M mutation, which remained unchanged from the baseline status (Figure 4A). Then, he began to receive treatment with erlotinib from December 2014. Unfortunately, after 3 mo, the disease progressed to the liver, and the patient developed dysphagia due to compression by enlarged mediastinal lymph nodes. He felt increasingly weak in the following days and developed cachexia.

Then, the frozen tissue was subjected to molecular testing by next-generation sequencing (NGS; NextSeq, Illumina), which confirmed the presence of an EGFR T790M mutation (allele frequency of 9.2%) in addition to the baseline exon 19 deletion mutation with an allele frequency of 70.2% (Figure 4B). From March 2015, the patient was administered with osimertinib at 80 mg PO QD. It is comforting that his dysphagia and Eastern Cooperative Oncology Group (ECOG) status gradually improved over the period of two weeks. Four months later, deglutition was restored to normal, and a partial response was achieved based on evaluation by chest computed tomography.

OUTCOME AND FOLLOW-UP

The patient’s ECOG status significantly deteriorated from January 2016, and 1 mo later, the patient died from disease progression in February 2016. The PFS was no more than 10 mo and the overall survival time was 29 mo. The patient did not receive CT scan from August 2015 to February 2016.

DISCUSSION

LSCC harbouring activating EGFR mutations are rare and even rarer for the coexistence of T790M mutations. This is a rare case of LSCC with coexistence of the EGFR exon 19 deletion and T790M mutation. Moreover, the patient benefited from osimertinib with a partial response. The overall survival time was 29 months. LSCC rarely harbours EGFR mutations, not to mention an acquired T790M
The primary tumor had a partial response to treatment with osimertinib. WBRT: Whole brain radiotherapy.

We review the previous literature that reports LSCC harbouring the T790M mutation (Table 1)[13-20]. To date, only 14 patients were reported in addition to the five LSCC patients enrolled in the clinical trials of the AURA series. Detailed TKI treatment information was available for only nine patients, of which five had LSCC transformation from adenocarcinoma[14,15,17,20]. The remaining three patients were acquired resistance cases after first-generation EGFR-TKI, but none were treated with third-generation EGFR-TKI[15,17]. It is worth noting that patient 5 received another third-generation EGFR-TKI, rociletinib[20]. However, this patient had an LSCC transformation derived from adenocarcinoma with de novo T790M detected at baseline. Furthermore, osimertinib has been proven by the FDA and is probably more potent than rociletinib[21]. As far as we are aware, this is the first reported T790M-related acquired resistant LSCC case with response to osimertinib, which serves as direct evidence of the effectiveness of osimertinib in LSCC.

In this case of LSCC, we observed a secondary T790M mutation of EGFR, contributing to the acquired resistance to first-generation EGFR inhibitors. This means that T790M is also an important mechanism for acquired resistance in LSCC. However, it is a key issue if this was a pure LSCC or not. Sometimes adenosquamous carcinoma or cancer with a mixture of other components may be mistakenly diagnosed as LSCC. It was reported that tests of multiple biopsies are helpful for accurate pathological and molecular diagnosis[22]. In this study, two biopsies of separate sites at different times and subsequent multiple serial sections were examined. Both of the results supported an identical diagnosis of LSCC with an EGFR exon 19 deletion mutation (Figure 3). Moreover, diagnosis by cytological examination of the bronchus and sputum also supported the LSCC diagnosis. In addition, imaging characteristics and long-term smoking history also supported this diagnosis. There was no evidence of coexistence with other components in multiple biopsies that were collected at multiple time points using multi-detection methods, so we consider this patient to have pure LSCC.

Previous research has suggested that the EGFR pathway in LSCC may be different from that in adenocarcinoma[23]. The PFS of patients receiving first-line gefitinib is about 8 mo. Although it is higher than the median PFS of our previous study, it is still obviously lower than that in adenocarcinoma[9]. Our case suggests that the EGFR pathway in LSCC may be different from that in adenocarcinoma[23].
pathway may be different between lung adenocarcinoma and LSCC. But it still warrants investigation in large clinical trials.

Previous reports revealed that the threshold of ARMS-PCR was at least 1% for detecting a mutant allele fraction, whereas that for NGS was as low as 0.04%23. In this case, the second biopsy specimen was analysed for \textit{EGFR} mutation by ARMS-PCR and NGS separately; however, the \textit{EGFR} T790M mutation was only detected by NGS, which was attributed to the higher sensitivity of NGS24 and lower degradation rate of DNA stored in liquid nitrogen. We foresee that NGS will play a more important role in \textit{EGFR} T790M detection in the future.

**CONCLUSION**

In summary, our findings highlighted that \textit{EGFR} T790M is also an important mechanism of acquired resistance for LSCC and offered direct evidence of the effectiveness of osimertinib in LSCC patients with the T790M mutation. Novel detection methods, such as NGS and better preservation conditions, hold promise for the more sensitive detection of the \textit{EGFR} T790M mutation.

**ACKNOWLEDGMENTS**

The authors are very grateful to Dr. Yi-Xi Chen for helpful comments on language editing, and Jing Zhang from Burning Rock Medical Examination Institute Co., Ltd for her technical help with genomics.
| Case ID | Age / sex | Smoker | Stage | Morphology | Sampling method | Anatomic site | EGFR mutation | Targeted therapy | Treated response | Progres-ssion time (mo) | Samp-lying method | Anatomic site | EGFR mutation | 3rd generation TKI | Ref. |
|---------|-----------|--------|-------|------------|----------------|---------------|---------------|-----------------|------------------|---------------------|-----------------|---------------|---------------|-----------------|------|
| 1       | 63/F      | Never  | IV    | ADC        | PE             | RUL           | WT1           | Erlotinib       | PR               | 22                  | B               | RUL           | SCC           | No Bugano et al [1] |     |
| 2       | NA        | NA     | IV    | SCC        | B              | NA            | Exon 19 deletion | Erlotinib       | NA               | 10                  | B               | NA            | SCC           | NA Masago et al [8] |     |
| 3       | 48/F      | Never  | IV    | SCC        | B              | RUL           | p.L747_P753>S  | Gefitinib       | PD               | 2                   | B               | RUL           | SCC           | No Grazia no et al [13] |     |
| 4       | 70/F      | Never  | IV    | SCC        | B              | LUL           | L858R         | Gefitinib       | SD / PR2         | 4                   | B               | Liver         | SCC           | No Grazia no et al [13] |     |
| 5       | 64/F      | Never  | IV    | ADC        | B              | RL            | L858R + T790M  | Gefitinib       | SD               | 10                  | B               | RL            | SCC           | L858R + T790M Rocletinib Harata et al [17] |     |
| 6       | 74/F      | Former | IV    | ADC        | B              | LL            | L858R         | Gefitinib       | PR               | 10                  | B               | LL            | SCC           | L858R + T790M No Jukna et al [14] |     |
| 7       | 79/F      | Never  | IV    | ADC        | PE             | RLL           | p.E746_A750del | Gefitinib       | PR               | 15                  | B               | RL            | SCC           | L858R + T790M No Jukna et al [14] |     |
| 8       | 52/M      | Former | IA    | ADC        | EB             | LUL           | L858R         | Gefitinib       | SD               | 12                  | B               | Pleura        | SCC           | L858R + T790M No Ding et al [12] |     |
| 9       | 53/M      | Former | IIIA  | SCC        | B              | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Na et al [15] |     |
| 10      | 65/M      | Never  | IB    | SCC        | B              | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Na et al [15] |     |
| 11      | 50/F      | Never  | IIA   | SCC        | B              | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Na et al [15] |     |
| 12      | 71/F      | Current| NA    | SCC        | EB             | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Ou et al [16] |     |
| 13      | 60/F      | Current| NA    | SCC        | EB             | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Ou et al [16] |     |
| 14      | 72/M      | Current| NA    | SCC        | EB             | NA            | T790M         | NA             | NA               | NA                  | NA              | NA            | NA            | NA Ou et al [16] |     |
| 15      | 63/M      | Former | IV    | SCC        | B              | RLL           | Exon 19 deletion | Gefitinib / erlotinib | PR / SD3       | 8                   | B               | RLL           | SCC           | p.E746_A750del Na et al [17] | Osimer tinib Current article |

1 Low cellularity in cytological samples.
2 SD In the lung and PR in liver metastases.
3 PR to gefitinib and SD to erlotinib. ADC: Adenocarcinoma; B: Biopsy; EB: Excisional biopsy; LL: Left lobe; LUL: Left upper lobe; NA: Not available; PE: Pleural effusion; PD: Progression disease; PR: Partial response; RL: Right lobe; RLL: Right lower lobe; RUL: Right upper lobe; SD: Stable disease; SCC: Squamous cell carcinoma.
Figure 4  Pathological and gene alteration analyses of the two biopsies. Amplification refractory mutation system-polymerase chain reaction test only detected exon 19 deletion in both samples (A), whereas next-generation sequencing detected the presence of an EGFR T790M mutation in addition to the exon 19-deletion mutation (p.E746_A750del) of the re-biopsy sample (B). NGS: Next-generation sequencing; ARMS-PCR: Amplification refractory mutation system-polymerase chain reaction.

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