Clinical Case Report

T790M mutation positive squamous cell carcinoma transformation from EGFR-mutated lung adenocarcinoma after low dose erlotinib
A case report and literature review

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Abstract

Rationale: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely used for the treatment of EGFR mutation positive advanced nonsmall cell lung cancer (NSCLC); however, acquired resistance is known to develop during these treatments. Among these mechanisms, histological transformation is seldom encountered. Although platinum based chemotherapy has been reported to be effective in the treatment of patients with small cell lung cancer transformation, there is a lack of information on the treatment of patients with squamous cell carcinoma (SQ) transformation.

Patient Concerns and Diagnosis: An 80-year-old nonsmoking woman was referred to our hospital because of an abnormal shadow on her chest radiograph. Diagnostic bronchoscopy was performed and pathological examination revealed adenocarcinoma. Mutation analysis of the EGFR gene revealed deletion of E746-A750 in exon 19. She refused both surgical treatment and radiation therapy, and preferred periodic radiologic follow-up. Unfortunately, approximately a year and a half after the initial diagnosis, the primary lesion enlarged, and many pleural nodules were newly detected (clinically T4N2M1a, stage IVA).

Interventions and Outcomes: Based on EGFR mutation analysis, a reduced dose of daily erlotinib was prescribed, which achieved a partial response and 34 months of progression-free survival (PFS). A repeated biopsy with an endobronchial cryoprobe was performed on the enlarged primary lesion. Pathological examination revealed SQ harboring an identical EGFR mutation with a secondary EGFR T790M mutation. Osimertinib 80 mg once a day was started as second line therapy, which resulted in 8 months of PFS and 15 months of survival.

Lesson: The literature review and our report suggest that osimertinib is a promising treatment for NSCLC regardless of histology if T790M is present as an acquired mutation.

Abbreviations: CEA = carcinoembryonic antigen; CT = computed tomography; CYFRA = cytokeratin 19 fragment; EBUS-GS = endobronchial ultrasonography with a guide sheath; EGFR = epidermal growth factor receptor; NGS = next-generation sequencing; NSCLC = non small cell lung cancer; PFS = progression free survival; SCC = squamous cell carcinoma related antigen; SCLC = small cell lung cancer; SQ = squamous cell carcinoma; TBB = transbronchial biopsy; TKI = tyrosine kinase inhibitor; TTF-1 = thyroid transcription factor 1.

Keywords: case report, histologic transformation, nonsmall cell lung cancer, Osimertinib, tyrosine kinase inhibitor

1. Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are widely used in EGFR mutation positive advanced nonsmall cell lung cancer (NSCLC). Tumors are known to acquire resistance to EGFR TKIs as first line treatment. In such circumstances, tumor rebiopsy is recommended as a second line therapy, especially after the failure of first or second generation EGFR TKIs. Two main types of resistance mechanisms to EGFR mutated NSCLC are “on target” and “off target” resistance. The former is the secondary alteration in the target oncogene, including either a second site mutation that promotes TKI resistance or the amplification or loss of the targeted oncogene. The EGFR T790M mutation is found in >50% of patients with acquired resistance to early generation EGFR TKIs, which occurs at a conserved “gatekeeper” threonine residue within the ATP binding pocket. EGFR T790M mutation is sensitive to osimertinib as a second

Consent: We obtained written informed consent from the patient for the publication of this case report and any images used. A copy of the written consent is available.

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line therapy. The latter is a tumor cell alteration occurring in proteins other than the targeted oncoprotein, which includes downstream signaling pathways and parallel bypass signaling pathways.

Histologic transformation is a type of resistance mechanism that is not a feature of “on target” nor “off target” mechanisms. It can alter tumor cell susceptibility to the inhibition of target oncoproteins. Small cell lung cancer (SCLC) transformation is seen in approximately 3% to 14% of NSCLC cases after first-line EGFR TKI treatment.[4,6] In such cases, cytotoxic drugs are commonly used according to the histologic findings. However, transformation to squamous cell carcinoma (SQ) is rare, and a standard therapy has not yet been established. We herein report an EGFR T790M mutation positive lung adenocarcinoma that showed histologic transformation to SQ after erlotinib treatment; thus demonstrating the efficacy of osimertinib. The pharmacokinetics of osimertinib were also investigated in this patient. The purpose of this report is to propose a method for the clinical management of T790M mutation positive SQ transformation from EGFR-mutated lung adenocarcinoma through our patient.

2. Case

An 80-year-old nonsmoking woman was referred to our hospital because of an abnormal shadow on her chest radiograph in January 2015 during an annual health check-up. She was asymptomatic and was treated for hypertension and bronchial asthma. Computed tomography (CT) of the chest revealed a nodular shadow in the right lower lung (S8) measuring 26 mm, accompanied by pleural indentation. Diagnostic bronchoscopy was performed using endobronchial ultrasonography with a guide sheath (EBUS-GS) transbronchial biopsy (TBB). Pathological examination revealed adenocarcinoma with napsin A, and the patient tested positive for thyroid transcription factor 1 (TTF-1) and negative for p40 (Fig. 1A–1D). Based on the International Association for the Study of Lung Cancer TNM (8th ed) clinical stages, the patient was diagnosed with stage IB (clinically T2aN0M0) lung cancer. Mutation analysis of the EGFR gene using the cobas® EGFR Mutation Test v2 kit (Roche Molecular Systems, USA) revealed that tumor cells harbored an identical EGFR mutation (deletion E746-A750 in exon 19) with the primary lesion after the initiation of osimertinib treatment. According to the EGFR mutation analysis, osimertinib 80 mg once a day was started as second line therapy, which resulted in a partial response in 2 months of survival from the beginning of osimertinib treatment. The enlarged primary lesion after the initiation of osimertinib is shown in Figure 2E. The steady state trough concentration of repeated doses of osimertinib at 40 mg every other day was 446.5 nM (Table 1).[7,8]

3. Discussion

We encountered a patient who showed transformation from adenocarcinoma to SQ after first line erlotinib treatment and had a significant response to second-line osimertinib treatment. Proper dose reduction of osimertinib in response to adverse events was also proven by measuring the drug concentration.

Figure 1. Histology of endobronchial ultrasonography with a guide sheath transbronchial biopsy before erlotinib therapy (A–D). (A) Hematoxylin and eosin (200x). (B) Napsin A (400x), (C) TTF 1 (400x) and (D) p40 staining (400x). Histology of rebiopsy with cryoprobe after erlotinib therapy, suggesting squamous cell transformation (E–H). (E) Hematoxylin and eosin (200x), (F) Napsin A (100x), (G) TTF 1 (100x) and (H) p40 staining (100x).
Although transformation from adenocarcinoma to SQ is uncommon, more cases are being reported.\[9\] However, its treatment has not yet been standardized. Previous studies have reported poor prognoses in cases that showed transformation from EGFR mutated advanced lung adenocarcinoma to SQ.\[10\] In our patient, although histologic examination of rebiopsy revealed SQ, panel based next-generation sequencing (NGS) showed EGFR T790M mutation. Eventually, the patient survived for 15 months from the initiation of osimertinib treatment. This showed the importance of both rebiopsy and treatment selection based on gene profile.

As shown in Table 2,\[10–31\] a total of 27 cases of SQ transformation in EGFR mutated lung adenocarcinoma after treatment with EGFR TKIs have been reported. The ages of these patients were 40 to 80 years (median age was 62 years), and 18 patients (66.7%) were female. All patients had EGFR mutations, 15 (55.6%) patients had an exon 19 deletion; 10 (37.0%) patients had an L858R point mutation; and 2 (7.4%) patients had other minor mutations. The T790M mutation was detected in only 1 case (3.7%) at the first diagnosis. These characteristics were not significantly different from those of known treatment naïve EGFR mutated NSCLC without SQ transformation in previous reports.\[32,33\] Moreover, the time from EGFR-TKI initiation to SQ transformation was 4 to 116 months (median duration, 18 months), indicating a trend toward a slightly longer treatment period than that known for EGFR-mutated NSCLC.

The positive rate of T790M during the treatment of 27 cases was 59.3%, which was similar to that in a previous report.\[3\] Osimertinib use after SQ transformation was observed in 40.7% of the 11 patients. The median survival time was estimated to be at least 8 months. In addition, the median survival time was at least 6 months in patients without osimertinib, suggesting that the effect of osimertinib is likely underestimated. These findings suggest that, unlike small cell carcinoma transformation,\[34\] driver-mutation specific treatment strategies may be beneficial for survival in SQ transformation.

Moreover, we measured the steady state trough concentration of osimertinib when it was prescribed at 40 mg every other day (Table 1). Its concentration was 446.5 nM, which was higher than that which was previously reported (318 nM) at 80 mg every day.\[8\] In this patient, prolonged high drug concentrations could induce gastrointestinal adverse events such as diarrhea and anorexia. This suggests that dose reduction and individualization are required for osimertinib treatment.

Table 1
The steady state trough concentration of erlotinib and osimertinib.

| Treatment   | Dose          | The steady state trough concentration measured (nM) | The steady state trough concentration previously reported (nM)\[7,8\] |
|-------------|---------------|---------------------------------------------------|---------------------------------------------------------------|
| Erlotinib   | 25 mg         | 428.4                                             | 620.0                                                         |
| Osimertinib | 80 mg         | N/A                                               | 318                                                           |
|             | 40 mg         | N/A                                               | 183                                                           |
|             | 40 mg every other day | 446.5                                           | N/A                                                           |

4. Conclusions
This case report and literature review highlighted the importance of confirming the genetic profile of EGFR mutated lung adenocarcinoma showing SQ transformation as resistance to EGFR TKI, and treatment with individualized EGFR TKI doses. We propose osimertinib is eligible for the treatment of SQ transformation from EGFR-mutated lung adenocarcinoma with T790M mutation.
### Table 2
Clinical characteristics of patients with squamous cell carcinoma transformation after resistance to epidermal growth factor receptor tyrosine kinase inhibitors.

| No. | Case | Age, Sex | Smoking | Original EGFR mutation | Response | Chemotherapy before SQT | Second histology | Duration from TKI initiation to SQT | Acquired gene alterations | Use of osimertinib as subsequent therapy | Survival from SQT |
|-----|------|----------|---------|------------------------|----------|--------------------------|----------------|---------------------------------|------------------------|----------------------------------|------------------|
| 1   | Scher et al[11] 2011 | 58, F | Former | Del19 | N/A | Erlotinib 9 m | + SQ | 20 m | T790M | N/A |  |
| 2   | Hsieh et al[12] 2015 | 51, F | Never | Del19 | PR | Gefitinib 4 m | – | SQ | 4 m | T790M | N/A |  |
| 3   | Hsieh et al[12] 2015 | 61, F | Never | L858R | PR | Gefitinib 12 m | + SQ | 22 m | T790M | N/A |  |
| 4   | Levin et al[13] 2015 | 66, F | Never | Del19 | PR | Erlotinib 8 m | + SQ | 8 m | T790M | N/A |  |
| 5   | Kulper et al[14] 2015 | 63, F | Never | L858R | N/A | Erlotinib 5 m | + SQ | 6 m | PIK3CA exon20 T790M | >6 m |  |
| 6   | Jukna et al[15] 2016 | 74, F | Former | L858R | PR | Gefitinib 10 m | – SQ | 10 m | T790M | N/A |  |
| 7   | Jukna et al[15] 2016 | 79, F | Never | Del19 | PR | Gefitinib 19 m | – SQ | 19 m | T790M | N/A |  |
| 8   | Haratani et al[16] 2016 | 48, F | Never | Del19 | N/A | Gefitinib 24 m | + SQ | 30 m | T790M | N/A |  |
| 9   | Haratani et al[16] 2016 | 64, F | Never | L858R, T790M | N/A | Gefitinib | + SQ | N/A | T790M | N/A |  |
| 10  | Okabe et al[17] 2017 | 69, M | Former | Del19 | PR | Erlotinib 12 m | – SQ | 12 m | T790M | N/A |  |
| 11  | Longo et al[18] 2017 | 43, F | Former | L858R | PR | Gefitinib 8 m | – SQ | 9 m | S768I T790M | >2 m |  |
| 12  | Bruno et al[19] 2017 | 44, F | Former | Del19 | PR | Afatinib 18 m | – SQ | 18 m | T790M | N/A |  |
| 13  | Park et al[20] 2017 | 40, M | Current | Del19 | PR | Afatinib 24 m | + SQ | 24 m | T790M | N/A |  |
| 14  | Izumi et al[21] 2018 | 68, F | Former | L858R | PR | Erlotinib 9 m | + SQ | 11 m | T790M | N/A |  |
| 15  | Kong et al[22] 2018 | 64, F | Never | L858R | PR | Afatinib 8 m | + SQ | 15 m | T790M | N/A |  |
| 16  | Shinohara et al[23] 2018 | 62, M | Never | L858R | N/A | Gefitinib 4 m | + SQ | 4 m | T790M | N/A |  |
| 17  | Yao et al[24] 2018 | 41, M | Current | Del19 | PR | Gefitinib 15 m, Osimertinib | + SQ | 31 m | mTOR amplification | >10 m |  |
| 18  | Sato et al[25] 2018 | 52, F | Former | Del19 | PR | Erlotinib 12 m | + SQ | 17 m | T790M | N/A |  |
| 19  | Yamaguchi et al[26] 2019 | 73, M | Former | Del19 | PR | Afatinib 10 m | – SQ | 10 m | T790M | N/A |  |
| 20  | Roca et al[27] 2019 | 67, F | N/A | L858R → T790M | PR | Gefitinib 58 m, Osimertinib 9 m | – SQ | 67 m | T790M | N/A |  |
| 21  | Chiang et al[28] 2020 | 54, F | Never | L833V, T790M | PR | Gefitinib 24 m, Osimertinib 19 m | + SQ | 116 m | T790M | N/A |  |
| 22  | Haruki et al[29] 2020 | 61, M | Former | Insertion19 | PR | Erlotinib 28 m | + ASQ | >42 m | T790M | N/A |  |
| 23  | Haruki et al[29] 2020 | 72, M | Former | L858R | PR | Erlotinib 9 m | – ASQ | >9 m | T790M | N/A |  |
| 24  | Haruki et al[29] 2020 | 56, F | Never | Del19 | PR | Gefitinib 72 m | + ASQ | 72 m | T790M | N/A |  |
| 25  | Hakozaki et al[30] 2020 | 70, F | Never | Del19 | N/A | Gefitinib, Erlotinib | + SQ | N/A | T790M | N/A |  |
| 26  | Lee et al[31] 2020 | 44, M | Never | Del19 | N/A | Gefitinib 10 m, Osimertinib 30 m | + SQ | 45 m | T790M | N/A |  |
| 27  | This case | 80, F | Never | Del19 | PR | Erlotinib 34 m | – SQ | 34 m | T790M | N/A |  |

**Abbreviations:** ASQ = adenosquamous cell carcinoma, Del19 = exon 19 deletion, F = female, M = male, m = month, PR = partial response, SQT = squamous cell carcinoma transformation.

*Including 9 cases of platinum plus pemetrexed, 2 cases of tegafur uracil, 2 cases of gemcitabine, and 2 cases of vinorelbine.
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