An *EGFR*-mutated Lung Adenocarcinoma Undergoing Squamous Cell Carcinoma Transformation Exhibited a Durable Response to Afatinib

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Abstract:
Squamous cell carcinoma (SCC) transformation has been identified as a mechanism of resistance to first-generation epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs), gefitinib or erlotinib, in *EGFR*-mutated lung cancer. However, whether second- or third-generation TKIs can overcome resistance due to SCC transformation remains unclear. We herein report an *EGFR*-mutated lung adenocarcinoma undergoing transformation into SCC that exhibited a durable response to afatinib, which is a second-generation irreversible *EGFR*-TKI. We suggest that afatinib can be considered as a treatment option for *EGFR*-mutated tumor undergoing SCC transformation, particularly in the absence of a *T790M* mutation.

**Clinical Practice Point** Afatinib can be considered an option for *EGFR*-mutated tumor undergoing squamous cell carcinoma transformation.

**Key words:** erlotinib; afatinib, *EGFR* mutation, squamous cell carcinoma transformation

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Introduction

*EGFR*-targeted therapy with small molecules in patients with activating mutations in *EGFR* have shown dramatic initial responses (1, 2). Drug resistance inevitably occurs, and various resistance mechanisms have been identified, including the emergence of a secondary *T790M* mutation, the activation of other oncogenic pathways, and the histological transformation into small cell carcinoma (3). Recently, squamous cell carcinoma (SCC) transformation has also been identified as a resistance mechanism to first-generation *EGFR*-TKIs (4). However, whether or not second- or third-generation TKIs can overcome resistance resulting from SCC transformation is unclear.

We herein report an *EGFR*-mutated lung adenocarcinoma undergoing transformation into SCC that exhibited a durable response to afatinib, a second-generation irreversible *EGFR*-TKI, suggesting its potential against *EGFR*-mutated tumor undergoing SCC transformation.

Case Report

A 52-year-old Asian woman with a 21-pack-year smoking history and complaining of exertional dyspnea was referred to our Department of Respiratory Medicine from a clinic because of massive right pleural effusion (Figure A). Histopathological and molecular analyses of cell blocks prepared from right pleural fluid revealed adenocarcinoma, as demonstrated by malignant epithelial cells positive for thyroid transcription factor-1 (TTF-1) and negative for p40 (Figure B) and harboring an exon 19 deletion mutation in epidermal growth factor receptor (*EGFR*). We started combination therapy of erlotinib and bevacizumab, which resulted in a partial response.

Twelve months later, palpable metastasis at the right latissimus dorsi muscle occurred, showing disease progression. We changed the regimen to combination therapy of car-
metastatic lesion at the right latissimus dorsi muscle (white arrow). (B) The histopathological results demonstrate transformation from adenocarcinoma to squamous cell carcinoma (SCC). Cell blocks before treatment initiation showing adenocarcinoma, as characterized by malignant epithelial cells immunohistochemically positive for thyroid transcription factor-1 (TTF1) and negative for p40. A core needle biopsy after erlotinib and other treatment regimens showing an SCC, as characterized by keratin pearl formation (Hematoxylin and Eosin staining) as well as an immunohistochemical staining pattern indicative of SCC (p40-positive and TTF-1-almost-negative). CBDCA: carboplatin, PEM: pemetrexed, DTX: docetaxel, RT: radiation therapy.

Discussion

To our knowledge, the clinical courses of 12 *EGFR* mutated tumors with SCC transformation after *EGFR-TKI* treatment with or without *T790M* have been reported (4-12). In addition, a recent study that examined the types of *EGFR-TKI* resistance mechanisms in 224 consecutive cases reported SCC transformation in 5 (2.2%) cases (13). These studies suggested that SCC transformation is difficult to treat because of the unavailability of specific and efficient therapeutic drugs to overcome the acquired resistance through SCC transformation.

In the present case, treatment with afatinib, which is a second-generation irreversible *EGFR-TKI*, produced a durable response to a tumor undergoing SCC transformation...
even after multiple treatment lines including erlotinib and platinum doublet therapy. No prior data on the efficacy of afatinib for the treatment of lung cancer with SCC transformation were available (4-12). However, a phase II study that evaluated the efficacy of afatinib in patients treated with gefitinib and/or erlotinib described modest antitumor effects, with a response rate of 8.2% (14). In addition, a study has shown afatinib to be more effective than erlotinib as a second-line treatment for patients with advanced SCC (15). Furthermore, a study retrospectively reviewing patients with EGFR-mutated squamous cell carcinoma treated with EGFR-TKIs as first-line therapies revealed that afatinib was effective in two of two cases, while gefitinib was not effective in two of two cases (16). From these and the present case findings, we suggest that afatinib can be considered as a treatment option for EGFR-mutated tumors undergoing SCC transformation, particularly those without T790M mutation.

In most cases, first-generation EGFR-TKIs were used before the occurrence of SCC transformation (4-9, 11, 12). Recently, a report showed that afatinib treatment also caused SCC transformation (10). The existence of differences in the frequencies of SCC transformation between different generations of EGFR-TKIs should be examined, given the difficulty in treating tumors undergoing SCC transformation.

There are some limitations associated with interpreting the findings in the present case. First, we cannot exclude the possibility of mixed tumors, particularly because the initial pathologic diagnosis was made using cell blocks of pleural effusion. Second, and importantly, according to the definition of acquired resistance to EGFR TKIs proposed by Jackman et al. (17), SCC transformation in the present case does not meet one of their criteria, which is “no intervening systemic therapy between cessation of gefitinib or erlotinib and the initiation of new therapy.” The muscle metastasis emerged during the initial erlotinib treatment. However, we did not rebiopsy this lesion immediately after erlotinib treatment, instead obtaining a pathological diagnosis of SCC from the same site after several other treatments. Thus, it is possible that SCC transformation in our case did not directly contribute to the acquired EGFR-TKI resistance.

In summary, we herein described a durable, sustained efficacy of afatinib in a patient with an EGFR-mutated adenocarcinoma undergoing SCC transformation, suggesting its potential to serve as a treatment option for this type of tumor.

The authors state that they have no Conflict of Interest (COI).

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