Clinical Response to Everolimus of EGFR—Mutation-Positive NSCLC With Primary Resistance to EGFR TKIs

Hiromichi Matsuoka,1 Hiroyasu Kaneda,2,3 Kazuko Sakai,4 Atsuko Koyama,1 Kazuto Nishio,4 Kazuhiko Nakagawa2

Clinical Practice Points

- We describe an effect of everolimus in a patient with epidermal growth factor receptor (EGFR)—mutation-positive non—small—cell lung cancer.
- Targeted resequencing showed mutations in tuberous sclerosis protein-complex 1 and 2.
- These mutations in tuberous sclerosis protein-complex 1 and 2 could confer marked primary resistance to EGFR tyrosine kinase inhibitors (TKIs).

- Mammalian target of rapamycin inhibitor could be able to overcome primary resistance to EGFR TKIs.
- Mammalian target of rapamycin is a valuable target for the treatment of non—small—cell lung cancer resistant to EGFR TKIs.

Keywords: EGFR mutation, EGFR-TKI to non-small cell lung cancer and mTOR, mTOR, Non-small cell lung cancer, Primary resistance

Introduction

Approximately 30% of patients with non—small—cell lung cancer (NSCLC) with EGFR-activating mutations develop primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), although EGFR TKIs demonstrate a clinical efficacy in EGFR—mutation-positive NSCLC.1 Mammalian target of rapamycin (mTOR) regulates cell growth, survival, and metabolism, and is targeted by the EGFR signaling pathway. It also plays a role in resistance to EGFR TKIs in lung cancer cells. A recent study found that mTOR is activated in human lung cancer positive for an activating EGFR mutation and that the extent of this activation is increased after acquisition of the T790M mutation of EGFR, which confers EGFR TKI resistance. We now describe a pronounced antitumor effect of the mTOR inhibitor everolimus in a patient with EGFR—mutation-positive NSCLC and primary resistance to EGFR TKIs.

Case Report

A 71-year-old Japanese male former smoker, who underwent surgery for primary renal cell carcinoma (T3bN0M0, stage III) 5 years previously, presented with recurrent disease in the form of metastases in both lungs. He received sunitinib as first-line treatment and achieved a partial response. However, 16 months later, a computed tomography scan revealed a lung tumor in the ostial region of the right upper lobe bronchus as well as mediastinal lymphadenopathy. Everolimus (10 mg once daily) was administered as second-line treatment for renal cell carcinoma, but, despite regression of the tumor, everolimus therapy was discontinued 1 month after its initiation because of the development of interstitial pneumonitis. Tumor growth resumed during treatment of the pneumonitis, resulting in obstructive pneumonia with deterioration of symptoms. Bronchoscopy revealed that the tumor had an exophytic lesion protruding into the lumen of the ostial region of the right upper lobe bronchus (Figure 1A). A pathologic diagnosis of primary lung cancer (T4N2M1b, stage IV) was based on the cells testing positive for cytokeratin (CK) 7 by immunostaining, whereas they were negative for CK20 and CK15.

Mutation analysis revealed that the tumor was positive for L858R and negative for T790M of the EGFR gene. Gefitinib (250 mg once...
daily) was therefore administered as first-line treatment. Two weeks later, a computed tomography scan revealed tumor progression. Gefitinib was changed to erlotinib (150 mg once daily), but the tumor developed further within 2 weeks (Figure 1B). Treatment with a reduced dose of everolimus (5 mg once daily) was initiated, and 1 month later, a significant response had been achieved with improvement of symptoms (Figure 1C). This response persisted for more than 3 months.

**Discussion**

Despite the benefits of EGFR TKIs for treatment of EGFR—mutation-positive NSCLC, all such treated patients ultimately develop drug resistance. Emergence of the T790M mutation is responsible for about 60% of acquired resistance to EGFR TKIs. A recent study found that this mutation also occurs in 25.2% of EGFR TKI-naive patients with NSCLC as well as in 31.5% of EGFR TKI-treated patients before such treatment. The presence of T790M before EGFR TKI treatment may thus predict primary resistance to these drugs.3

MTOR controls cell growth, metabolism, and survival. It is also targeted by EGFR signaling and contributes to EGFR TKI resistance in lung cancer cells. A recent study revealed that mTOR is activated in human lung cancer positive for an activating EGFR mutation and that the extent of this activation is increased after acquisition of the T790M mutation. Acquired resistance to afatinib and cetuximab has also been associated with mTOR activation in patients with EGFR—mutation-positive NSCLC negative for T790M.5 Rapamycin and everolimus are mTOR inhibitors and prevent tumor progression, prolong survival, and ameliorate EGFR TKI resistance in mouse models of NSCLC, suggesting that mTOR inhibitors may have antitumor effects and may be able to overcome primary or acquired resistance to EGFR TKIs in patients with EGFR—mutation-positive NSCLC. A phase II study with unselected patients with advanced NSCLC who manifested tumor

**Table 1** Mutations in TSC1 and TSC2 Identified by Targeted Resequencing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Type</th>
<th>Amino Acid</th>
<th>Tumor</th>
<th>Pre-TKI</th>
<th>Post-TKI</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1</td>
<td>chr9</td>
<td>Missense</td>
<td>p.Asp569Asn</td>
<td>+</td>
<td>–</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>TSC2</td>
<td>chr16</td>
<td>Missense</td>
<td>p.Ile1561Met</td>
<td>+</td>
<td>+</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>TSC2</td>
<td>chr16</td>
<td>Missense</td>
<td>p.Ala1700Val</td>
<td>+</td>
<td>+</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TKI = tyrosine kinase inhibitor; TSC = tuberous sclerosis protein-complex.
progression during EGFR TKI treatment revealed a response rate of 2.3% for everolimus monotherapy. However, only 11 of 85 patients were evaluated for EGFR mutation status, and no such mutations were detected.

We investigated the mechanism of the antitumor effect of everolimus in this patient. Targeted resequencing in tumor biopsy specimens prior to initiation of gefitinib identified some mutations in tuberous sclerosis protein-complex 1 and 2 (TSC1/TSC2) (Table 1). A recent study also reported that PI3K/Akt/mTOR pathway alterations identified using targeted sequencing were associated with de novo resistance to gefitinib in patients with NSCLC with activating EGFR mutations. Given that the present patient with EGFR—mutation-positive NSCLC manifested pronounced and rapid tumor regression to everolimus treatment but failed to respond to prior EGFR TKI therapy, these mutations in TSC1/TSC2 could confer marked primary resistance to EGFR TKIs in EGFR—mutation-positive NSCLC. As far as we are aware, this is the first report of a favorable effect of everolimus on an EGFR—mutation-positive NSCLC tumor.

**Conclusion**

Here, we have reported genomic alteration in TSC1/TSC2 identified in a tumor specimen from a patient with NSCLC with activating EGFR mutations whose tumor developed primary resistance to EGFR TKIs. We suggested that this mutation in TSC1/TSC2 could be conferring resistance to EGFR TKIs because this patient responded to the mTOR inhibitor everolimus, but not EGFR TKIs.

Further investigation to define the clinical benefit of mTOR inhibitors for NSCLC with primary or acquired resistance to EGFR TKIs is thus warranted.

---

**Disclosure**

The authors have stated that they have no conflicts of interest.

**References**