To the Editor:

EGFR-Activating Mutation

Patients Harboring an

BRAF Can Be Harmful in Dual Inhibition of EGFR and 

NSCLC patients with EGFR-activating mutations even before the arise of the EGFR T790M mutation.1 In addition to the EGFR T790M mutation, either mutations, amplifications, or fusions of the genes affecting downstream and parallel signaling pathways constitute the remainder of the EGFR TKI resistance cases.2 These include oncogenic mutations in the genes encoding KRAS, NRAS, MEK, and PIK3CA proteins;

Table 1. Cytokine Levels in Serum before Tocilizumab Administration

<table>
<thead>
<tr>
<th>Value for our patient, pg/mL</th>
<th>MIP-1α</th>
<th>IL-1α</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IP-10</th>
<th>IL-1β</th>
<th>SDF-1α</th>
<th>IL-1RA</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>MIP-1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal reference value, &lt;pg/mL</td>
<td>68.1</td>
<td>45.8</td>
<td>8.2</td>
<td>7.2</td>
<td>51.6</td>
<td>725.7</td>
<td>1639</td>
<td>&lt;2.6</td>
<td>6.3</td>
<td>2020</td>
<td>39.3</td>
</tr>
</tbody>
</table>

MIP-1α, macrophage inflammatory protein-1α; IL-1α, interleukin-1α; IP-10, alias symbol for CXCL10 [C-X-C motif chemokine ligand 10]; IL-1RA, interleukin 1 receptor type 1; TNF-α, tumor necrosis factor-α; SDF-1α, stromal cell-derived factor 1α (alias symbol for CXCL12 [C-X-C motif chemokine ligand 12]); TNF-α, tumor necrosis factor-α; IFN-γ, interferon gamma; MIP-1β, macrophage inflammatory protein-1β.

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References

Dual Inhibition of EGFR and BRAF Can Be Harmful in Patients Harboring an EGFR-Activating Mutation

To the Editor:

EGFR tyrosine kinase inhibitors (TKIs) are widely used to treat patients with non-small-cell lung carcinoma (NSCLC) who have mutations that activate the tyrosin kinase EGFR. Although EGFR-TKI treatment appears to be effective in reducing tumor mass in the beginning of therapy, the tumor eventually develops a resistance in most EGFR-NSCLC patients. Notably, a mutation altering a second site in the EGFR protein, T790M, accounts for the majority (~60%) of the resistance to both the first-generation EGFR TKIs (e.g., gefitinib and erlotinib) and the second-generation EGFR TKIs (e.g., afatinib). Accordingly, the third-generation EGFR-TKI, osimertinib, was developed to target the EGFR T790M mutation and was recently approved as the “first-line” treatment for NSCLC patients with EGFR-activating mutations even before the arise of the EGFR T790M mutation.1

In addition to the EGFR T790M mutation, either mutations, amplifications, or fusions of the genes affecting downstream and parallel signaling pathways constitute the remainder of the EGFR TKI resistance cases.2 These include oncogenic mutations in the genes encoding KRAS, NRAS, MEK, and PIK3CA proteins;
amplifications of the genes encoding MAPK, HER2, and MET proteins; and fusions of the genes encoding ALK, FGFR3, NTRK1, and RET proteins with a gene of high-level expression. Thus, combined treatment of EGFR TKIs with relevant inhibitors could provide a reasonable option to overcome the resistance.

Recent studies have shown that the serine/threonine kinase BRAF is activated due either to BRAF V600E mutation or to gene fusion in a subset of patients who are resistant to EGFR TKIs. Notably, such BRAF activation has not been reported in EGFR TKI treatment-naive patients but detected only in patients with an acquired EGFR TKI resistance, suggesting that BRAF activation can be selected de novo during EGFR TKI therapy. Hence, dual inhibition of EGFR and BRAF might be a reasonable treatment option to block the potential, unwanted activation of BRAF pathway, which could result from EGFR TKI therapy in the absence of prior BRAF activation. How potent or safe this approach is, however, remains unknown.

Thus, we examined the treatment effect of the BRAF inhibitor dabrafenib on the growth of such NSCLC cell lines as A549 (EGFR wild-type), H1650 (EGFR ex19del), HCC827 (EGFR ex19del), and PC9 (EGFR ex19del) in the presence or absence of the EGFR TKI afatinib. We noted that dabrafenib alone has little effect on the growth of all the cell lines with EGFR wild-type or the activating mutation ex19del (Fig. 1). Co-treatment of dabrafenib and afatinib, however, reversed the afatinib-mediated growth repression of the cell lines with the EGFR ex19del mutation (Fig. 1). This effect was not observed in the EGFR wild-type cell line A549, suggesting a role for the constitutively high EGFR activity and/or afatinib sensitivity in opposing the afatinib-mediated growth repression by dabrafenib. We suggest that care should be taken in developing a strategy of simultaneously inhibiting EGFR and BRAF in treating NSCLC patients.

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Nintedanib Effect in Osimertinib-Induced Interstitial Pneumonia

To the Editor:

Osimertinib is an oral, potent, irreversible third-generation EGFR tyrosine kinase inhibitor (TKI) approved for the treatment of EGFR-positive NSCLC patients. Although osimertinib has shown significant efficacy in EGFR-mutant patients with NSCLC, severe adverse events such as interstitial lung disease (ILD) have been reported in a few patients and even case deaths.1,2 Currently, the underlying pathogenesis of EGFR TKI-induced ILD remains unclear. Common treatments encompass targeted therapy discontinuation and hormone therapy. However, there are limited therapies for patients unsuitable for hormone therapy. Herein, we report the first successful treatment of nintedanib in an EGFR L858R-mutant NSCLC patient who was diagnosed as osimertinib-induced interstitial pneumonia.

An 84-year-old Chinese female ex-smoker presented with a pulmonary mass in the left lobe discovered on computed tomography (CT) scan. Biopsy on pleural effusions and subsequent amplification-refractory mutation system – polymerase chain reaction for EGFR analysis led to the diagnosis of advanced lung adenocarcinoma with EGFR L858R mutation. The patient started osimertinib 80 mg once daily as first-line therapy and achieved partial response. However, she developed deteriorating chest distress and shortness of breath after 5 months of osimertinib treatment. A CT scan of the chest revealed extensive patchy shadows in both lungs. Therefore, the patient discontinued osimertinib immediately and received 1 week of empirical antibiotic treatment at local hospital. Simultaneous laboratory test did not identify pathogens. CT scans after antibiotic therapy did not show improvement (Fig. 1A). Considering that no pathogen was detected and CT manifestation was consistent with osimertinib-induced ILD, osimertinib-induced interstitial pneumonia was diagnosed. Because the patient was gerontic with a history of diabetes, hormone therapy was not considered in case of hyperglycemia and infection. Nintedanib has been approved for treatment of idiopathic pulmonary fibrosis.3 Given its antifibrotic activity, nintedanib 150 mg twice daily was prescribed. CT scans after 2 weeks of nintedanib monotherapy showed obvious improvement in both lungs without tumor progression (Fig. 1A). The patient felt better overall and remained on nintedanib treatment. CT scans after 4 weeks of nintedanib commencement still showed stable disease control (Fig. 1A). Because the overall condition had improved, the patient withdrew nintedanib and started gefitinib monotherapy with good tolerance.

Severe ILD has been reported in patients with targeted therapy including osimertinib, gefitinib, and crizotinib.1,4,5 There is no optional treatment for patients who are diagnosed with targeted therapy–related interstitial pneumonia and are unsuitable for hormone therapy. Herein, our case preliminarily shows dramatic effect of nintedanib in a patient with osimertinib-induced interstitial pneumonia. Although osimertinib was discontinued immediately after the diagnosis of pneumonia, the patient did not experience cancer progression within 1 month of nintedanib treatment. To the best of our knowledge, this case is the first to provide evidence of nintedanib effect in patients with interstitial pneumonia induced by EGFR TKIs.

In conclusion, this case initially proves nintedanib effective in EGFR TKI–induced interstitial pneumonia, providing a new promising strategy for a subset of patients with targeted therapy–induced pneumonia, especially for those unsuitable for hormone therapy.

References