Tocilizumab for Fulminant Programmed Death 1 Inhibitor-Associated Myocarditis

To the Editor:

As the use of immune checkpoint inhibitors (ICIs) is increasing for multiple cancer types, reports of fatal ICI-associated myocarditis are also increasing. Strong immune suppressors, such as alemtuzumab and antithymocyte globulin, have been successfully used in several cases of severe myocarditis. However, the safety of these immunosuppressors is another challenge, as a number of patients die of infection.

A 74-year-old woman with lung squamous cell carcinoma (T4N2M0, IIIIB) received pembrolizumab (200 mg) as her second-line therapy. On day 18 after the first administration, the patient experienced low back and thigh muscle pain. Two days later, she experienced development of ptosis and tightness in her chest. Her electrocardiogram (ECG) showed polymorphous ventricular rhythm of tachycardia. Echocardiography indicated that the ejection fraction of the left ventricle was less than 40%. Her serum creatine kinase (CK) level and troponin 1 level peaked at 21,378 (normal range 24–170) U/L and 25.73 (normal range 0–0.056) μg/L, respectively, and her N-terminal pro-b type natriuretic peptide level increased to 8783 pg/mL. The clinical diagnosis was ICI-associated myocarditis and myositis. The patient began receiving 1 g of pulse methylprednisolone for 3 days and 20 g of intravenous immunoglobulin immediately. In the first 48 hours, her CK and cardiac troponin 1 (cTnI) levels decreased slightly, but her ventricular tachycardia continued, and heart failure was obviously aggravated. Respiratory failure, hypotension, and oliguria developed, and the patient had to be intubated at 36 hours. At the same time, she experienced development of pulmonary infection. Serum detection showed significant increases in the levels of various cytokines, including interleukin-6 (IL-6) and IL-8 (Table 1). Tocilizumab (8 mg/kg) was administered at 48 hours. On the fifth day, an ECG showed paroxysmal sinus rhythm. However, during the next week, life-threatening cardiac arrhythmias consisting of alternating ventricular tachycardia, atrial fibrillation, and other abnormal heart rhythms persisted, with more severe myasthenia. Pneumonia was another serious problem complication, because her respiratory muscles were very weak. Analysis of her sputum revealed Klebsiella pneumonia. Because her CK and cTnI levels were decreasing gradually and her pulmonary infection was becoming more severe, methylprednisolone was tapered (80 mg for 7 days, then 40 mg); no other immunosuppressor was given. After tracheotomy and administration of antibiotics and effective support therapy, at 4 weeks, her CK and cTnI levels decreased to normal, an ECG showed sinus rhythm, and the ejection fraction of her left ventricle increased to more than 60%. The patient’s temperature was normal. The symptoms of myositis (muscular weakness) progressively decreased.

The patient experienced development of myocarditis manifested as life-threatening ventricular arrhythmia and cardiac failure. Her condition continued to deteriorate despite early pulse therapy. A stronger immunosuppressor was necessary but was contraindicated because of serious infection. A significant increase in her levels of multiple serum cytokines, including IL-6 (which is crucial for enhancing immune attacks), was noted. Tocilizumab, a humanized monoclonal antibody against IL-6 receptors, has been shown to be beneficial for management of adverse events secondary to other types of immunotherapy. To our knowledge, this is the first reported case of successful treatment of severe programmed death 1 inhibitor–associated myocarditis by using tocilizumab. Furthermore, its safety has been well documented, with a low risk of infection. In our patient, tocilizumab showed good efficacy and safety for near-fatal myocarditis. Tocilizumab combined with glucocorticoids might potentially be a first-line treatment option for severe ICI-associated myocarditis, though more research is needed.

Hanping Wang, MD
Department of Respiratory Medicine
Peking Union Medical College Hospital
Beijing, People’s Republic of China

Ran Tian, MD
Peng Gao, MD
Department of Cardiology
Peking Union Medical College Hospital
Beijing, People’s Republic of China

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Li Zhang, MD, Department of Respiratory Medicine, Peking Union Medical College Hospital, No.1 Shuai Fu Yuan, Dong Cheng District, Beijing 100730, People’s Republic of China. E-mail: zhanglipumch1026@sina.com

© 2019 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.09.080
To the Editor:

EGFR-Activating Mutation Patients Harboring an BRAF Can Be Harmful in Dual Inhibition of EGFR and Patients and collected and analyzed the data, performed Wang, Tian, Qian Wang, Gao, and Zhang treated the pa-

Critical Review of the Letter

Qian Wang, MD
Department of Rheumatology
Peking Union Medical College Hospital
Beijing, People’s Republic of China

Li Zhang, MD
Department of Respiratory Medicine
Peking Union Medical College Hospital
Beijing, People’s Republic of China

Acknowledgments
This work was supported by the National Key Research and Development Program of China (grant 2016YFC0901500). Drs. Hanping Wang, Tian, and Zhang designed the study and wrote this letter. Drs. Hanping Wang, Tian, Qian Wang, Gao, and Zhang treated the patients and collected and analyzed the data, performed a critical review of this letter, and gave their final approval.

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;

Table 1. Cytokine Levels in Serum before Tocilizumab Administration

<table>
<thead>
<tr>
<th>Value</th>
<th>MIP-1α</th>
<th>IL-1α</th>
<th>IL-1β</th>
<th>IL-10</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-13</th>
<th>IL-17A</th>
<th>IFN-γ</th>
<th>MIP-1β</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<tr>
<td>8</td>
<td>21</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>45</td>
<td>102</td>
<td>206</td>
<td>30</td>
<td>5</td>
<td>620</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>218</td>
</tr>
</tbody>
</table>

MIP-1α, macrophage inflammatory protein-1α; IL-, interleukin-; 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-β, tumor necrosis factor-β; IFN-γ, interferon gamma; MIP-1β, macrophage inflammatory protein-1β.

Drs. Oh and Lim contributed equally.

Address for correspondence: Jeong-Seon Ryu, MD, PhD, Center for Lung Cancer, Inha University Hospital, Department of Internal Medicine, Inha University Hospital, 27, Inhang-ro, Jung-Gu, Incheon, 22332, South Korea. E-mail: jsryu@inha.ac.kr

© 2019 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.09.085