Pemetrexed-Induced Fluid Retention

To the Editor:

Despite the favorable toxicity and safety profiles of pemetrexed (Alimta; Eli Lilly and Company, Indianapolis, IN), several adverse events have been reported, including blood and lymphatic system disorders, gastrointestinal disorders, and general disorders.¹–³ In this letter, we describe a case series consisting of seven patients who developed clinically significant fluid retention, an uncommon adverse effect associated with the use of pemetrexed. All patients have received vitamin supplementation and were pre-treated with corticosteroids as indicated in the package insert (Table 1).

Other causes of edema were excluded, and all patients had normal echocardiogram, normal levels of B-type natriuretic peptide and albumin, normal renal, hepatic, and thyroid function tests, and no significant proteinuria. Most patients presented with mild-to-moderate edema, mainly in periorbital area, as illustrated in Figure 1 (case 1). Of the seven cases, only one patient (case 4) developed grade 3 refractory edema with symptomatic bilateral effusion. A bilateral thoracentesis was necessary for symptom relief, and the pleural effusion analysis was consistent with an exudate with no malignant cells. A bilateral thoracentesis was necessary for symptom relief, and the pleural effusion analysis was consistent with an exudate with no malignant cells. Multiple thoracenteses were performed and only in case 1 did the pleural effusion persist and necessitate parietal pleurectomy. A bilateral thoracentesis was necessary for symptom relief, and the pleural effusion analysis was consistent with an exudate with no malignant cells. Multiple thoracenteses were performed and only in case 1 did the pleural effusion persist and necessitate parietal pleurectomy.

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REFERENCES

Safety of Concomitant Administration of Seasonal and/or H1N1 Flu Vaccination in Patients Receiving Erlotinib for Advanced Non-small Cell Lung Cancer

To the Editor:

Patients with advanced tumors are at higher risk of acquiring and dying from infections, because of a weaker immune system, among other factors.¹ For this reason, Centers for Disease Control and Prevention guidelines strongly recommend flu vaccination in cancer patients older than 50 years. Moreover, the pandemic distribution of H1N1 virus led to the preparation of new vaccines, which should be used in this setting.²

Patients with advanced non-small cell lung cancer (NSCLC) are often adequate candidate for flu vaccination because of chronic respiratory disease, advanced age, and poor performance status. Efficacy of H1N1 influenza vaccination in this subgroup of patients seemed to be comparable with that from healthy volunteers.³ Although safety and immunogenity of influenza vaccines in patients receiving chemotherapy have been extensively investigated, no data on safety of vaccines in patients with NSCLC treated with epidermal growth factor receptor tyrosine kinase inhibitors are available.

Erlotinib (Tarceva) is a humanized monoclonal anti-epidermal growth factor receptor tyrosine kinase inhibitor of broad spectrum and is approved for the first-line treatment of patients with advanced NSCLC with evidence of partial response.⁴ It is also approved as maintenance therapy following failure of platinum-based chemotherapy. In the case of patients who develop resistant disease to erlotinib, progression of disease is generally rapid and supportive care is focused on symptom control. Although safety and immunogenity of influenza vaccines in patients receiving chemotherapy have been extensively investigated, no data on safety of vaccines in patients with NSCLC treated with epidermal growth factor receptor tyrosine kinase inhibitors are available.

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hair growth, facial erythema, and several forms of frontal alopecia. On the other hand, the most common influenza vaccine side effects are tenderness and pain in the site of injection. For this reason, in the suspect that the concomitant administration of erlotinib and seasonal and/or H1N1 vaccination could be burdened by severe reactions, we decided to analyze the incidence of local and systemic side effects in our series.

So far, we evaluated 14 patients treated with erlotinib for advanced NSCLC who received 11 administrations of seasonal vaccine (Fluarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) and seven of H1N1 vaccine (Focetria; Novartis, Inc., Basel, Switzerland). Data were collected in a median time of 30 days (range, 15–45 days) from vaccination by telephone interviews to avoid the omission of unsolicited reports.

All patients were receiving erlotinib (150 mg: 6 patients; 100 mg: 8 patients) since ~12 months (range, 1–32 months). Six patients had grade 1 skin rash, one had alopecia grade 1, and one had vaginal mucositis grade 1 before vaccine administration.

Neither local nor systemic adverse events were recorded after the vaccination, except for one patient who referred a grade 1 pain in the site of injection lasting for 1 day and for another who had skin rash.

### TABLE 1. Patients Characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Comorbidities</th>
<th>Regimen</th>
<th>No. of Cycles at Edema Onset</th>
<th>Edema Localization</th>
<th>Grade</th>
<th>Edema Treatment</th>
<th>Continued on Pemetrexed</th>
<th>Actual Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>None</td>
<td>Carboplatin and pemetrexed (first line)</td>
<td>7</td>
<td>Eyelid and ankle</td>
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<td>No</td>
<td>Yes</td>
<td>Pemetrexed maintenance</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>F</td>
<td>None</td>
<td>Pemetrexed (second line)</td>
<td>13</td>
<td>Generalized (facial, peripheral, and pleural effusion)</td>
<td>II</td>
<td>Yes</td>
<td>Yes</td>
<td>Pemetrexed</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>Hypertension, chronic obstructive pulmonary disease, and pulmonary embolism</td>
<td>Carboplatin and pemetrexed (second line)</td>
<td>13</td>
<td>Peripheral</td>
<td>II</td>
<td>Yes</td>
<td>Yes</td>
<td>Pemetrexed maintenance</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>None</td>
<td>Carboplatin, pemetrexed, and bevacizumab (first line)</td>
<td>14</td>
<td>Generalized (facial, peripheral, and pleural effusion)</td>
<td>III</td>
<td>Yes</td>
<td>No</td>
<td>Erlotinib and bevacizumab</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>F</td>
<td>Depression</td>
<td>Pemetrexed and bevacizumab (third line)</td>
<td>16</td>
<td>Facial</td>
<td>I</td>
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<td>Yes</td>
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<tr>
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<td>74</td>
<td>M</td>
<td>Diabetes</td>
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<td>6</td>
<td>Peripheral</td>
<td>II</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>None</td>
<td>Pemetrexed and bevacizumab (second line)</td>
<td>8</td>
<td>Ankle</td>
<td>I</td>
<td>No</td>
<td>Yes</td>
<td>Pemetrexed and bevacizumab</td>
</tr>
</tbody>
</table>

*Common Terminology Criteria for Adverse Events v 3.0 (CTCAE).*