Complement Activation and Rituximab Distribution in CNS NHL—Letter

Silvia Hofer1,2, Karin Mengele3, Manfred Schmitt3, Bernhard Pestalozzi1, and Stefan Aebi2

We have read with great interest the article by Kadoch and colleagues (1). Their pharmacokinetic model indicates rapid distribution of intraventricular rituximab from cerebrospinal fluid (CSF) into neural tissues and serum. These findings may have more general implications for intrathecal (IT) immunotherapy with monoclonal antibodies. IT trastuzumab was safe and effective in HER2-positive leptomeningeal carcinomatosis in a pooled analysis of several case reports (2). On the basis of our own data of trastuzumab concentrations in serum and corresponding CSF levels, we have suggested that IT trastuzumab at a 3-weekly dose of 150 mg is effective against leptomeningeal carcinomatosis (3).

Here, we report serum and CSF concentrations and clinical outcome of 3 consenting patients with leptomeningeal carcinomatosis from HER2-positive breast cancer treated with IT trastuzumab. All patients had prior whole brain radiotherapy for brain metastases but no need for radiotherapy for bulky leptomeningeal carcinomatosis. The time from first IT therapy to CSF clearance of malignant cells was 3, 2, and 1 months, respectively. Normalization of the meningeal contrast enhancement by MRI occurred after 4 months in 2 patients and after 3 months in one. The performance status improved substantially in all 3 patients. To date, one patient has died 12 months after the onset of leptomeningeal carcinomatosis due to a relapse after 10 months of response. The second patient died of cervical cancer 20 months after the onset of leptomeningeal carcinomatosis from breast cancer without evidence of leptomeningeal carcinomatosis recurrence. The third patient is in very good condition and in clinical and radiological complete remission 22 months after diagnosis of leptomeningeal carcinomatosis. So far, overall 45 IT trastuzumab applications have been performed uneventfully.

Table 1. Trastuzumab concentrations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Cumulative IT trastuzumab (mg)</th>
<th>CSF trough concentration (ng/mL), range (n)</th>
<th>Serum trough concentration (ng/mL), range (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>1,860</td>
<td>840–1,872 (10)</td>
<td>61,951–224,992 (8)</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>2,700</td>
<td>55–404 (6)</td>
<td>912–3,923 (5)</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>1,950</td>
<td>104–138 (5)</td>
<td>30,493–46,915 (5)</td>
</tr>
</tbody>
</table>

NOTE: Patient 1: intrathecal dose escalation and concomitant intravenous trastuzumab as described in Fig. 1 of ref. 3. Serum trough levels were taken at the same time as the CSF samples, i.e., before IT trastuzumab. Abbreviation: n, number of CSF and serum samples.

Disclosure of Potential Conflicts of Interest

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