Tumor Markers in Monitoring Response to Chemotherapy for Patients with Gastric Cancer

Hisanao Ohkura, Ibaraki Prefectural Central Hospital and Ibarakiken Regional Cancer Center, Ibaraki, Japan

Evaluating chemotherapy by measuring tumor size is sometimes impossible in patients with diffusely spreading cancer, where elevated tumor markers often seem to reflect the tumor burden and the effect of a treatment. In germ-cell tumors, hepatomas, prostatic carcinomas and endocrine tumors, the tumor cells produce and release disease-specific markers: human chorionic gonadotropin (hCG), α-fetoprotein (AFP), prostate specific antigen (PSA) and each hormone, respectively. These markers are used not only in screening and diagnosis for these diseases but also in monitoring patients under treatment, including chemotherapy. However, in other common carcinomas, such as of the breast, lung and gastrointestinal tract, tumor markers are used but not routinely in evaluating treatments, because of their lower association rates in resectable cancers, their frequent 'non-specific' elevation in benign diseases and marker-producing and non-producing heterogenic tumor cells, and of this there was no reliable evidence. Since the guidelines of the American Society of Clinical Oncology (1), no circulating tumor marker has been validated as a surrogate marker.

TUMOR MARKERS USED IN GastrIC CANCER

In gastric cancer, carcinoembryonic antigens (CEA), carbohydrate antigens of the sialyl-Lewis A group such as CA19-9, those of the sialyl-Tn group such as CA72-4 and STN, those of the sialyl-Lewis X group such as sialyl-SSEA-1 (SLX) and NCC-ST-439 and CA125 are known to be elevated in serum in advanced disease (Table 1). At stage IV of the disease, most of them are elevated in 30-76% of patients; however, none of them is elevated in more than 40% of patients with resectable disease (2,3). It is well known that undifferentiated types of gastric cancer seldom produce these markers. Although not produced by gastric cancer cells and with no relation to the histological subtypes, CA125 is usually elevated in serum when the disease has invaded the serous membrane and the peritoneal cavity (4).

Preoperative serum markers, especially CA19-9, CA72-4 and CEA, have been evaluated as indicators of advanced disease and shorter prognosis and some of them have been confirmed as being significant prognostic factors, next to the three major factors of depth of invasion (T), lymph node metastasis (N) and distant metastasis (M) (3,5). Therefore, these markers are used in predicting and in monitoring patients with advanced gastric cancer.

Table 1. Positive rates of serum markers in gastric cancer by stages

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut-off</th>
<th>No. of patients</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>5 ng/ml</td>
<td>1612</td>
<td>I 5.2</td>
</tr>
<tr>
<td>CA19-9</td>
<td>37 U/ml</td>
<td>210</td>
<td>I 2.9</td>
</tr>
<tr>
<td>NCC-ST-439</td>
<td>7 U/ml</td>
<td>210</td>
<td>I 4.8</td>
</tr>
<tr>
<td>CA72-4</td>
<td>4 U/ml</td>
<td>36</td>
<td>I 0</td>
</tr>
<tr>
<td>STN</td>
<td>4 ng/ml</td>
<td>40</td>
<td>I 0</td>
</tr>
<tr>
<td>CA125</td>
<td>35 U/ml</td>
<td>50</td>
<td>I 0</td>
</tr>
<tr>
<td>AFP</td>
<td>20 ng/ml</td>
<td>1874</td>
<td>I 0.6 (I + II)</td>
</tr>
</tbody>
</table>

Modified from ref. 1.

EVALUATION OF SERUM TUMOR MARKERS IN CHEMOTHERAPY

In the recently proposed RECIST criteria (6), tumor markers are indicated only for the evaluation of non-target lesions such as CR, non-CR/non-PD and PD. Tumor markers alone cannot be used to assess response, but could be used to confirm complete response. Specific additional criteria for standardized usage of PSA and CA-125 response in support of clinical trials are being developed. However, in this issue of JO, Yamao and his colleagues' study evaluated retrospectively serum CEA, CA19-9 and CA125 in monitoring of patients with gastric cancer under chemotherapy (7). They found a significant correlation between the decrease or increase in circulating tumor markers with the clinical response determined by the change of tumor size. They defined the criteria of responders by tumor marker as showing a 50% or more drop in tumor marker level for more than 4 weeks and compared with the tumor response evaluated by imaging diagnosis with the criteria of the World Health Organization (WHO). This is the first evidence demonstrating the accuracy and usefulness of serum markers to correlate with imaging diagnoses and with prognosis in patients with gastric cancer under chemotherapy.

DECREASED CIRCULATING TUMOR MARKER AS A SURROGATE END-POINT OF CHEMOTHERAPY

In the recent clinical trials with marimastat, a new matrix metalloproteinase inhibitor, circulating tumor markers were
used as surrogate indicators of antitumor activity (8). Six studies of colorectal, ovarian and prostate cancer have been completed and pooled analysis demonstrated a dose-dependent biological effect, with a 50% decrease of tumor markers as defined by the authors. Effects on tumor markers were associated with increased survival. Ongoing phase III studies are investigating the effects of marimastat in addition to chemotherapy in the treatment of small cell lung cancer and pancreatic and gastric carcinoma.

FUTURE PERSPECTIVE

As Yamao et al. stated in their discussion, patients do not always have measurable lesions and clinicians sometimes have to evaluate tumor response based on a subjective medical judgement from clinical symptoms and laboratory data. Circulating tumor markers may be a clue to a breakthrough in this area. Further evaluation with large-scale prospective studies is needed to confirm these results. According to the RECIST criteria, tumor markers alone cannot be used to assess response, but could be used to evaluate non-target lesions such as CR, non-CR/non-PD and PD and to confirm complete response. Gastric cancer patients with non-measurable lesions but with elevated tumor markers could be enrolled in future clinical trials and then the validity of these markers could be tested.

References