Initial Assessment of Tumor-Associated Antigen CA-125 in Patients with Ovarian, Cervical, and Testicular Tumors

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Serum CA-125, a glycoprotein antigen, has been measured in serum of patients with ovarian cancer, cervical cancer, or nonseminomatous germ-cell tumor of testis. Increased concentrations were found in 21 of 27 patients with epithelial ovarian cancer and two of three patients with ovarian teratoma. Changes in CA-125 concentrations in serum during chemotherapy mirrored the progress of the disease as assessed by clinical and radiological evidence. Although CA-125 provides no real asset for diagnosis, it should have value as a marker for monitoring response to chemotherapy.

Additional Keyphrases: glycoprotein antigen • cis-platinum analog JM8 • epithelial tumor of ovary • chemotherapy • cancer

Owing to its histological complexity, the ovary gives rise to benign and malignant tumors of epithelial, stromal, and germ-cell origin (1). Epithelial tumors (serous, endometrioid, mucinous, clear-cell, and undifferentiated) account for about 94% of ovarian carcinoma. A monoclonal antibody has recently been developed by somatic hybridization of spleen cells from mice immunized with human epithelial ovarian carcinoma cell lines (2). The nonspecific antigen defined by this antibody, CA-125, is associated with a high-molecular-mass glycoprotein that is expressed in coelomic epithelium during embryonic life (3). Several antigens have been detected in ovarian carcinoma (4–8), but for most patients with ovarian carcinoma, a clinically useful antigenic marker has yet to be found. We measured CA-125 concentrations in serum from patients with epithelial and germ-cell tumors of the ovary, cervical carcinoma, and nonseminomatous germ-cell tumor of testis, to evaluate its use as a marker for monitoring progress of the disease during chemotherapy.

Patients and Method

Concentrations of tumor-associated antigen CA-125 were measured in serum from 22 healthy adult controls, 30 patients with ovarian cancer (27 with cystadenocarcinoma, stages I to IV, and three with teratoma, stages III to IV), 10 patients with cervical carcinoma (eight with carcinoma in situ, stages II and III, and two with invasive stage II disease), and 15 patients with advanced nonseminomatous germ-cell tumor of the testis (stages III and IV). All patients had histologically proven disease. The tumors were classified according to the criteria of the British Testicular Tumor Panel (9) and The International Federation of Gynecology and Obstetrics (10). Twenty-seven patients with ovarian cystadenocarcinoma were monitored during treatment with the cis-platinum analog, JM8.

Blood samples were obtained from the 27 patients before treatment and weekly thereafter during therapy with JM8, the samples being stored at −20 °C until analysis. All analyses were performed in duplicate with the immunoradiometric assay kit from CIS (UK) Ltd. The assay has a dynamic range of 5–500 kilo-arb. units/L and analytical CV of <10%. Concentrations of CA-125 were expressed in arbitrary units based on comparison with a primary reference standard.

JM8 (diamine-1,1-cyclobutane dicarboxylate Pt(II); OBCDA; NSC 241240), from Bristol-Myers, Langley, Slough, SL3 6EB, U.K., is a second-generation platinum analog currently under investigation in a phase II clinical trial. Each patient was given JM8 intravenously, 400 mg per square meter of body surface, at four-weekly intervals. The drug, dissolved in 250 mL of a solution of 50 g of dextrose per liter of isotonic saline, was administered intravenously over 30 min. Patients with heavy prior treatment (more than six months of previous myelosuppressive chemotherapy) were treated with 90% of this dose (360 mg/m²).

Results and Discussion

Twenty-two healthy adults had serum CA-125 concentrations ranging from 8 to 32 kilo-arb. units/L with a median of 14 kilo-arb. units/L. Table 1 summarizes the serum CA-125 concentrations of the patients. With the upper limit of the healthy controls (32 kilo-arb. units/L) as the cutoff limit, 21 of 27 patients (78%) with epithelial ovarian carcinoma had values greater than this and 19 of the 27 (70%) had values exceeding 128 kilo-arb. units/L. Of the three patients with ovarian teratoma, two had values >32 kilo-arb. units/L and two patients with stage II disease cervical carcinoma had values >128 kilo-arb. units/L. All eight patients with carcinoma in situ had CA-125 concentrations within the normal reference interval, as did all 15 patients with advanced nonseminomatous germ-cell tumor of the testis.

Twenty-seven patients with epithelial tumors of the ova-

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| Table 1. CA-125 Concentrations in Serum of Patients with Cancer of the Ovary, Cervix, or Testis |
|----------------------------------|--------------|---------|---------|
| Type of Tumor | No. of cases | Range   | Median  | No. of cases with CA-125 |
| Healthy controls | 22 | 8–32 | 14 | 0 |
| Ovarian cystadenocarcinoma | 27 | 6–1100 | 265 | 21 |
| (Stages I–IV) | | | | |
| Ovarian teratoma (Stages III and IV) | 3 | 17–58 | 36 | 2 |
| Cervical carcinoma (CIN II and III) | 8 | 6–11 | 6 | 0 |
| Stage II disease | 2 | 335–400 | 367 | 2 |
| Nonseminomatous cell tumor of testis | 15 | 6–32 | 11 | 0 |

*Upper limit of CA-125 (kilo-arb. units/L) in the healthy controls.
ry, receiving treatment with JM8, were monitored each week, their progress being assessed on the basis of their clinical state and radiological evidence (CT scan). The pretreatment concentrations of tumor maker (CA-125) are summarized in Table 2, based on their histological classification; Figure 1 illustrates representative serial changes in serum CA-125 concentrations in three of the patients. In patient A the CA-125 concentration doubled in seven weeks, but decreased dramatically after the second JM8 treatment, reaching the reference interval about 16 weeks after starting treatment. This suggesting a good response to chemotherapy, as was confirmed at a second laparotomy.

In contrast, Patient B showed poor response to chemotherapy, in that clinical examination and scintigraphy showed no reduction in tumor size. An increase in abdominal girth with malignant ascites was accompanied by an increase in the CA-125 concentration, from 335 to 485 kilo-arc. units/L within 52 days.

Patient C showed clinical and radiological evidence of stable disease without change in tumor size. However, the CA-125 concentration decreased, remaining within normal values for two weeks, then increased again, after which treatment was stopped (Figure 1).

We consider these results an indication that CA-125 may be useful in the management of patients with epithelial carcinoma of the ovary. Unlike others (7, 11–14), we see no role of CA-125 in the diagnosis of ovarian malignancy, because this can only be properly made by the surgeon and histopathologist; moreover, at diagnosis, 20% of cases are likely to be CA-125 negative. However, measurement of this antigen is useful for detecting persistent and recurrent disease and for serving as a tumor marker to monitor patients undergoing treatment. It may help to define the optimum number of treatments of the timing and site of a second laparotomy, and the duration of maintenance treatment. CA-125 assay has advantages over other biochemical indices such as serum concentrations of enzymes and acute-phase proteins, all of which are nonspecific.

Table 2. Pretreatment Concentrations of CA-125 in Serum from Patients with Malignant Epithelial Tumors of the Ovaries

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
<th>&gt;32*</th>
<th>&gt;128</th>
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<tr>
<td>Serous</td>
<td>21</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Mucinous</td>
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<td>0</td>
</tr>
<tr>
<td>Clear cell</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endometrioid</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

*Upper limit of CA-125 (kilo-arc. units/L) in the healthy controls.

References