CORRESPONDENCE

Re: New Guidelines to Evaluate the Response to Treatment in Solid Tumors (Ovarian Cancer)

Rustin et al. (1) have summarized a simplification of the guidelines for the definition of response in ovarian cancer clinical trials proposed by the Gynecologic Cancer Intergroup. The guidelines state that “Patients are not evaluable by CA125 if they have received mouse antibodies...” We believe this advice merits careful scrutiny and further consideration (2).

Depending on the assay, the presence of human anti-mouse antibodies (HAMA) in the serum of patients can affect the accuracy of CA125 measurements to different degrees, as determined in several pilot studies (3,4). We used samples containing varying levels of potentially interfering HAMA to assess the performance of two commonly available automated clinical CA125 assay platforms. The Immulite 2000 CA125 assay (Diagnostic Products, Los Angeles, CA) uses a murine anti-CA125 monoclonal antibody to capture the CA125 in the serum sample and detects bound CA125 with a polyclonal rabbit anti-CA125 antibody. The AxSym CA125 assay (Abbott Laboratories, Abbott Park, IL) uses a sheep anti-CA125 polyclonal antibody to capture CA125 in the serum and detects CA125 with a monoclonal murine anti-CA125 antibody. Both assays incorporate a wash step before quantifying CA125 in the residual sample. We postulated that increasing concentrations of HAMA were more likely to influence the Immulite platform because of the possible binding of HAMA to the murine capture antibody.

A residual pooled serum sample from an oregovomab clinical trial (2) with a known high HAMA concentration was used to test the level of interference in both assays. This sample was serially diluted in normal human serum and enough purified CA125 (5) was added to each sample to yield a final CA125 concentration of approximately 100 U/mL. CA125 was quantified in parallel by two independent clinical pathology diagnostic laboratories. The assay results are shown in Table 1.

Absolute CA125 measurements in the spiked normal serum were similar using the two platforms. However, CA125 spiked into serum containing the two highest HAMA concentrations, 43,050 ng/mL and 14,347 ng/mL, resulted in noticeably lower CA125 measurements in the Immulite assay than in AxSym system, suggesting interference by the HAMA. In our experience with oregovomab administration in clinical studies, we have found that HAMA levels, as measured using the Immunomedics HAMA kit, peak (after four to eight injections) at less than 40,000 ng/mL in 95% of patients. We are unaware of other murine antibody applications likely to induce greater levels of HAMA than oregovomab. Results from this pilot study indicate that a universal effect of HAMA on CA125 measurement should not be assumed. HAMA and anti-idiotypic antibodies interfere less with assays that use polyclonal, non-murine capture antibodies, and a murine monoclonal detecting antibody than with assays that use the reverse antibody pairing (murine capture antibodies). It is appreciated that individual patient samples may contain other heterophilic antibodies that impact diagnostic test performance. Our findings suggest that, using appropriate assays, patients with previous exposure to murine antibodies for either diagnostic or therapeutic purposes may be reliably followed for tumor response by CA125 monitoring in both clinical trial and patient management settings.

We recommend that the same assay system be used for comparative serial monitoring of individual patients over time.

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REFERENCES


NOTES

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Table 1. CA125 assay results as a function of HAMA concentration

<table>
<thead>
<tr>
<th>HAMA, ng/mL</th>
<th>CA125 level in normal serum†</th>
<th>HAMA sample dilution†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No dilution</td>
<td>1:3</td>
</tr>
<tr>
<td>HAMA, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neg‡</td>
<td>43,050‡</td>
<td>14,347</td>
</tr>
<tr>
<td>AxSym§, U/mL</td>
<td>98</td>
<td>94.6</td>
</tr>
<tr>
<td>Immulite§, U/mL</td>
<td>98.5</td>
<td>52.7</td>
</tr>
</tbody>
</table>

*HAMA = human anti-mouse antibodies.
†All samples spiked with a constant volume of purified CA125 to ~100 U/mL.
‡HAMA concentrations were determined using the Immunomedics (Morris Plains, NJ) HAMA ELISA.
§Interassay variability at ~100 U/mL was determined by the manufacturer and confirmed by the clinical laboratory to be 5.3%–7.0% for the Abbott AxSym CA 125 assay and 5.3% for the DPC Immulite OM-MA assay.

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Taylor and Haverstick make an interesting observation that there was no interference in CA125 levels by HAMA when the AxSym CA125 assay (Abbott Laboratories, Abbott Park, IL) was tested, but there was interference when the ImmuLite 2000 CA125 assay (Diagnostic Products, Los Angeles, CA) was tested. Because of the potential interference with the CA125 assay by HAMA, the Gynaecologic Cancer Intergroup (GCIG) definition states that patients are not evaluable by CA125 if they have received mouse antibodies. We made this statement because most investigators would be unaware whether the assay used in their study could be influenced by HAMA. If investigators want to use the GCIG CA125 definition in patients who have received mouse antibodies, they should check whether their CA125 assay has been shown to be influenced by HAMA as demonstrated by Taylor and Haverstick. When reporting their results, investigators would need to state first that certain patients had received antibody infusions, and second, whether that antibody interfered with the CA125 assay used in those patients. Without those safeguards, results could be reported in which assays were used that were affected by prior exposure of the patient to mouse antibodies.

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