CA 125 in Ovarian Cancer: Advances and Controversy

Ovarian cancer continues to be a major health threat for women. The American Cancer Society estimates that in the United States in 1998, 25,400 new cases will be diagnosed and 14,500 women will die as a result of this disease (1). Most of these cancers are epithelial in origin, as germ cell tumors of the ovary represent only ~5% of the total. Approximately 70% of epithelial ovarian cancers will occur in women who are over the age of 50 years, and more than one-half of the women will be diagnosed with advanced disease. Thus, these women will have a 5-year survival rate of <30%. Certainly, there is great need for improved diagnostic methods to permit detection of this disease at an early stage, as well as more effective treatments for adenocarcinoma of the ovary.

CA 125, the first serum tumor marker test for epithelial cancer of the ovary, was introduced by Bast et al. in 1983 (3). The murine monoclonal antibody (OC125) that is used to detect the CA 125 antigen was obtained after immunization with the OVCA 433 cell line (4). The original CA 125 test used the OC125 antibody as both the capture and indicator antibody in a radioimmunometric assay. More recently, the CA 125 II test has been developed, which uses the M 11 monoclonal antibody as the capture antibody for CA 125. A recent epitope-mapping workshop conducted by the International Society of Oncodevelopmental Biology and Medicine (ISOBM) has defined the binding characteristics of monoclonal antibodies reactive with CA 125 and has identified two major regions on the antigen, which are called OC125-like and M 11-like epitopes (5). The CA 125 antigen is actually a heterogeneous mixture of glycoproteins with a molecular weight range of 200-1000 kDa, but lower molecular weight species have also been reported (6). Much of the heterogeneity of the CA 125 antigen is most likely related to differences in glycosylation. The antigenic domains reactive with the monoclonal antibodies appear to be located on the protein part of the CA 125 molecule. CA 125 antigen is a cell membrane glycoprotein expressed by a variety of epithelial cells, and it is present in the circulation of patients with a variety of cancers, most notably ovarian cancer. Approximately one-half of the patients who have localized (Stage 1) ovarian cancer and 90% of patients with advanced disease (Stages 2–4) have increased serum concentrations of CA 125 (5). The CA 125 antigen is not specific for ovarian cancer, as serum increases are observed in some patients with cancers of the breast, endometrium, gastrointestinal tract, and lung. Benign diseases of the uterus, liver, and gastrointestinal tract and benign tumors of the ovary and uterus are also associated with increased concentrations of serum CA 125 (6).

The lack of specificity of CA 125 for ovarian cancer has not hampered the use of the test in the clinical management of patients with this disease. Initially, the CA 125 test was approved for use postoperatively in patients to determine the likelihood that tumors would be found at a second-look operation (7). If the CA 125 value was increased after debulking surgery and completion of required courses of chemotherapy, residual disease was likely present and the patient would not benefit from this additional surgery. Since a “normal” CA 125 value (<35 kilounits/L, <35 units/mL) would not indicate the absence of disease, a second-look operation to confirm the disease status was recommended. Today, however, the use of second-look surgery is controversial, and a recent NIH Consensus panel has recommended the use of serial CA 125 testing in lieu of second-look surgery, at least for those women with a preoperative increase of CA 125 (8). The combined use of CA 125, physical and pelvic exam, and transvaginal ultrasonography can detect disease progression with 90% sensitivity (7). An optimal monitoring protocol has not been recommended, but suggested practice is to perform CA 125 testing every 3 to 4 months for 2 years posttreatment, and regularly but less frequently thereafter (8, 9).

In most studies, 35 units/mL (35 kilounits/L) is used as the upper limit of the normal reference range for CA 125. However, as shown by Sugiyama et al. (10), the performance characteristics (sensitivity, specificity, and positive and negative predictive values) for detection of disease can be significantly improved by lowering the cutoff value to 16.0 units/mL. The value of 16.0 units/mL was selected on the basis of that value being the upper limit of the normal reference range for postmenopausal women, which would be the expected value after ovariectomy. Other groups have also proposed that the cutoff value for CA 125 be set at a value lower than 35.0 units/mL when the test is used to monitor for disease recurrence in women who have had an ovariecotmy or hysterectomy, as the uterus is also a source of CA 125 (11, 12). Substantial data exist to warrant immediate implementation of the use of a lower cutoff value in routine patient care.

A developing role for the serum CA 125 test is that of assessing response to chemotherapy. Data supportive of treatment response is important for continuing a toxic therapy, especially for patients who have no clinically detectable disease. On the other hand, data indicating treatment failure can prompt early discontinuation of an expensive, noneffective therapy and provide the opportunity for salvage therapy or participation in a clinical trial of a new treatment. Rustin et al. (13) have reported a method to define treatment response on the basis of a CA 125 decrease. A computer-assisted calculation of serial CA 125 values obtained at appropriate intervals has defined the CA 125 treatment response as a 50% or 75% reduction of the postsurgical CA 125 value. More recently, Münsedt et al. (14) have suggested a less complicated assessment of CA 125 for defining treatment response. They defined a CA 125 treatment response on the basis of a CA 125 ratio (CA 125 value after chemotherapy ÷ CA 125 value at 4 weeks after surgery). A ratio of 0.1 correlated well with long-term survival. Clearly, additional validation of these
findings is required before either of these techniques can be used in clinical practice.

The use of CA 125 in screening for ovarian cancer is perhaps the most controversial aspect of CA 125. Screening of premenopausal women for ovarian cancer was not recommended by the NIH Consensus Panel, except for women who have a family history of a first degree relative with ovarian cancer or an individual who has one of the hereditary cancer syndromes. These women should have annual physical and pelvic exams, a CA 125 test, and a transvaginal ultrasonography (8). Screening of postmenopausal women with current diagnostic modalities has been criticized on the basis of the low positive predictive value resulting from the low sensitivity and the low specificity (high false-positive rate) of the screening program, and the observation that only about one-half of the early-stage ovarian cancer patients will have an increased CA 125 value. There is little benefit to the early detection of late-stage cancers (15). However, efforts at improving the performance of cancer screening is being attempted with the use of nonlinear algorithms (16) and multiple tumor marker tests (17). An ongoing prospective randomized controlled trial enrolling 120,000 postmenopausal women in the United Kingdom utilizes a CA 125 algorithm to prompt transvaginal ultrasonography; the preliminary results look promising (18).

The new clinical interest in CA 125 is occurring at the same time that many new assay formats for CA 125 are being made available to the clinical laboratory. The report by Davelaar et al. (19) in this issue of the Journal compares the analytical and clinical performance of five of these new test formats and compares them to the original and modified CA 125 II assays. Two important conclusions can be drawn from their data. First, these methods do not produce "equivalent" results. The linear regression analyses show proportional error (slope) and bias (intercept). The bias plots indicate that considerable differences in values can occur for some sera. The low-end bias for samples with values ≤35 units/mL is of special concern when clinical decisions are being made at 16, 20, 24, or 35 units/mL, as is under consideration in some of the clinical studies previously mentioned. Since most of these assays are using the same antisera, we can only conclude that these differences are related to the test methodology (matrix effects and reaction kinetics) and the heterogeneity of the CA 125 analyte.

The second observation is that all of the CA 125 methods produce highly concordant data, which result in accurate clinical interpretations. Note that in some instances, slight adjustment of the upper limit of the normal reference range may be necessary to correct for the low-end bias. We must also remember that test interferences related to the human anti-mouse or heterophile antibody may be responsible for outlier errors and that these errors may not be demonstrated equally by all methods. Finally, test methods that do not produce equivalent results should not be used interchangeably. As new test methods are introduced into the clinical laboratory, their clinical accuracy should be revalidated as is discussed in this report (19). In addition, we recommend that the assay method be listed on the CA 125 test report to alert the physician to possible bias relating to different test formats.

References

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