Special Review

Use of CA-125 in Clinical Trial Evaluation of New Therapeutic Drugs for Ovarian Cancer


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INTRODUCTION: THE PROBLEM OF OVARIAN CANCER

Ovarian Cancer Incidence and Mortality Rates. Ovarian cancer is the fourth leading cause of death from cancer in women and accounts for the highest mortality rate of all of the gynecological cancers (1). Despite aggressive treatment via radical surgery, radiotherapy, or chemotherapy, the mortality rate remains >50% for diagnosed patients. Although approximately 90% of stage IA (growth limited to the ovary) and 70% of stage IIA (metastases to the uterus or Fallopian tubes) tumors are curable if detected, 70% of women who are diagnosed with stage III and IV tumors have widespread intra-abdominal disease or distant metastases at diagnosis. For these patients, the overall cure rate for ovarian cancer has remained relatively constant during the last 20 years. Ovarian cancer has an overall cure rate of approximately 45%, a relatively discouraging prognosis.

Furthermore, the quality of life for many patients with ovarian cancer is compromised severely because only 20% of patients with advanced disease are long-term disease-free survivors. The remaining 80% will relapse, and many of these relapsing patients will receive second-, third-, fourth-, fifth-, or tenth-line therapies. New therapies are tested in relapsed patients, and better ways are needed to determine which of these patients should be selected for clinical trials.

Current Treatment. The standard first-line treatment for patients with ovarian cancer is a combination of carboplatin and paclitaxel (3). This regimen reflects collected wisdom from over 30 years of randomized, controlled clinical trials with various agents. Chemotherapy for ovarian cancer was first administered in the 1960s, following the synthesis of alkylating agents such as chlorambucil and melphalan. These compounds continued to be prescribed as single agents through the 1970s, although introduction of the platinum-based agent cisplatin in 1973 initiated a shift in treatment paradigms.

Although no hard evidence for an overall survival advantage with platinum-based compounds was demonstrated until the 1990s (4, 5), early studies revealed that cisplatin significantly improved disease-free survival and response rates when compared with then-standard treatments. Cisplatin was effective as a single agent and in combination regimens, resulting in the relatively popular first-line combination of cisplatin with cyclophosphamide.

The next major shift in therapy occurred in the early 1980s, with the development of carboplatin. Carboplatin proved equally efficacious (in single and combination therapy) but significantly less toxic than cisplatin (5). At standard doses, carboplatin has fewer adverse effects on kidneys, the nervous system, or the auditory system, and patients who receive carboplatin report reductions in nausea and vomiting relative to levels experienced with cisplatin. Because carboplatin-based regimens were significantly better tolerated than cisplatin-based therapies, single-agent carboplatin had effectively replaced cisplatin as the standard of care by the late 1980s (6).

The treatment paradigm shifted again in the 1990s with the introduction of paclitaxel (Taxol). An alkaloid ester derived from the bark of the Pacific yew tree (Taxus brevifolia), paclitaxel arrests the cell cycle by disrupting microtubule formation during mitosis (7). Several Phase II trials showed that paclitaxel was active in cases of relapsed ovarian cancer, including patients who were unresponsive to or concurrently receiving platinum-based treatments (8–13). These pivotal studies led to the administration of paclitaxel as a first-line therapy in combination with cisplatin (14, 15).

The acceptance of paclitaxel-cisplatin as the standard of care for ovarian cancer was established in two pivotal, large-scale trials that compared paclitaxel-cisplatin with cyclophosphamide-cisplatin regimens in patients with stage III–IV disease (14, 15). These studies proved the superiority of paclitaxel by demonstrating statistically significant differences in response rates, progression-free survival times, and median overall survival times. Subsequent trials demonstrated that carboplatin could be substituted for cisplatin to provide an equally efficacious but less toxic and better tolerated regimen (16–18). The failure of the very large ICON3 trial to demonstrate any superiority of paclitaxel plus carboplatin over carboplatin alone has led to many women in Europe being offered single-agent carboplatin (19).

The combination of paclitaxel with carboplatin remains the standard first-line treatment of ovarian cancer in many centers. However, evidence from recent Phase II trials suggests that docetaxel, a semisynthetic derivative of Taxol, confers equal...
benefit with less neurotoxicity than paclitaxel (20–22). Thus, docetaxel may prove to be a more viable agent for first-line treatment regimens in the near future.

Current Opportunities. Recent breakthroughs in our understanding of the molecular mechanisms of carcinogenesis and proliferation have resulted in the development of numerous molecularly targeted agents that inhibit signal transduction, angiogenesis, and other pathways. This increased understanding has led to the development of novel agents such as trastuzumab (Herceptin), a recombinant monoclonal antibody that has revolutionized treatment regimens for certain metastatic breast cancers (23–26), and the rationally designed tyrosine kinase inhibitor imatinib mesylate (Gleevec), which has transformed protocols for chronic myeloid leukemia (27, 28). These successes and the numerous drugs under development that target molecular lesions characterized in ovarian cancers provide a great opportunity to continue to improve the treatment of this disease.

Evaluation of new drugs for ovarian cancer has been hampered by difficulties in measuring i.p. disease; the tumor deposits associated with ovarian cancer are usually very difficult to clearly delineate by noninvasive techniques. This has significance for diagnosing early-stage disease, as well as measuring response to therapy. As stated, ovarian cancer is chemosensitive, and chemotherapy has impacted the curability for a fraction of patients. This result could be much improved with better methods to determine whether a tumor is responding to therapy in the early stages of treatment. Because aggressive chemotherapy is accompanied by drug toxicity, which lowers the quality of life for the patient, and because it is difficult to monitor the response of ovarian carcinoma to therapy, a serum biomarker such as CA-125 has great potential for optimizing both therapeutic regimens and clinical trials in which they are tested.

Inadequacies of Current Clinical Trial Designs. End points currently used in clinical trials for ovarian cancer include survival, progression-free survival, and objective tumor response associated with the administration of anticancer agents. However, each of these end points presents unique difficulties when applied to clinical trials for ovarian cancer. Current clinical trial designs do not allow optimal dosing, scheduling, and duration of drug therapy because of difficulties in making timely measurement of disease response to therapy by noninvasive methods. The development of better measures of tumor response would not only aid clinical trial design and conduct but would also provide guidance for individualized therapy with approved drugs because, when treating individual patients, difficulties in measuring response can lead to overtreatment of nonresponsive disease with toxic therapy and reduced quality of life for the patient. In this section, we present some of the issues that hamper current clinical trial design.

Defining the end point is one of the most crucial, yet most difficult, issues in trial design for ovarian cancer therapy. Although survival is the ultimate end point of all clinical trials for ovarian cancer, it may require a lengthy time to obtain and may be affected by therapeutic interventions other than the therapy under investigation. Progression-free survival from start of treatment to clinical progression has therefore become an increasingly important end point when evaluating drug combinations because it may be obtained earlier and is unaffected by therapies subsequent to the trial therapy. However, if the therapies under comparison are of different duration, progression-free survival becomes a less robust end point and can create uncertainty about results, particularly if used to discontinue a trial prematurely (29). In one major trial, the use of progression as an end point was compromised by the introduction of second-line therapy, in many cases because of a rise in CA-125 before the date of clinical progression had been reached (30). Without clinical evidence of progression, the date of progression becomes difficult to determine, thus leading to a diverse and inconsistent set of methods to classify such patients.

In addition to using survival parameters as end points, researchers have attempted to measure objective response of a tumor to therapy for more than 40 years (31, 32). In 1979, the WHO published classifications and criteria of tumor response designed to standardize measurements for solid cancers (33, 34). Although these criteria have been widely used, shortcomings have resulted in a number of modifications and clarifications to the WHO definitions by such organizations as the Eastern Cooperative Oncology Group (35) and the Gynecologic Oncology Group (36). To address these issues, the Response Evaluation Criteria in Solid Tumors (RECIST) Group recently proposed guidelines to evaluate the response to treatment in solid tumors (37). Whereas the RECIST criteria address many shortcomings of previous attempts to codify tumor response, they have limited utility in the evaluation of ovarian cancer. The RECIST criteria define progression on the basis of evaluation of measurable disease, and therefore response rate, as defined by RECIST, applies only to patients who present with measurable disease, which precludes its use in almost 50% of ovarian cancer patients.

Because it varies as a function of prognostic factors as well as drug efficacy, to use response rate as an end point in a clinical trial, the patient group must be defined (e.g., those who relapse <6 months, 6–12 months, and >12 months after platinum therapy). To maximize the benefits of therapeutic regimens being tested in future clinical trials for ovarian cancer, an objective, reliable, and meaningful measure is required to assess end points.

CA-125 AS A SURROGATE END POINT IN CLINICAL TRIALS OF OVARIAN CANCER CHEMOTHERAPEUTICS

Characteristics of CA-125. Characterized in 1981, the CA-125 antigen (38) remains the only serum tumor marker routinely used to test for epithelial cancer of the ovary (39). CA-125 is a membrane glycoprotein expressed by epithelial cells of different origins and thus is present in the serum of patients who have a variety of tumors. Different sites of glycosylation on CA-125 produce a heterogeneous mixture of varying molecular mass (mostly >1000 kDa) glycoproteins (40).

The first method developed to measure CA-125 was a radioimmunometric assay that used the murine monoclonal antibody OC 125 as both capture and indicator antibodies (39). OC 125 was obtained after immunization with the OVCA 433 cell line, which was derived from the ascites fluid of a patient with papillary cystadenocarcinoma of the ovary (38). OC 125 recog-
nizes the CA-125 epitope on a high molecular weight glycoprotein designated MUC16. Monoclonal antibodies raised against other epitopes expressed by this molecule have led to the development of the CA-125-II assay, a variant of the original CA-125 assay that utilizes the M11 monoclonal antibody as the capture antibody (41, 42). Both assays have proved reliable for measuring CA-125 levels in a number of benign and cancerous conditions, most notably ovarian cancer.

Several studies document the similarities of sensitivity and specificity obtained with the original CA-125 and newer CA-125-II assays (43, 44). In addition to the very high correlation to the original CA-125 assay, the CA-125-II assay exhibits significantly less day-to-day variation and has better measurement characteristics for low CA-125 values (45). For the purposes of monitoring response to therapy, higher CA-125 values are generally observed and (over time) can be measured more precisely with the CA-125 II assay.

CA-125 concentration is elevated most consistently in epithelial ovarian cancer, and its value has been demonstrated as a marker for patient prognosis, disease progression, and response to chemotherapy. At diagnosis, approximately 50% of patients who have stage I ovarian cancer and 90% of those with advanced-stage disease have elevated concentrations of CA-125 in their sera (2, 41, 46). However, CA-125 is expressed by a number of different cell types, both cancerous and noncancerous. Some patients with cancers of the lung, breast, endometrium, and gastrointestinal tract present elevated levels of CA-125, and CA-125 levels are also elevated in endometriosis, benign diseases of the liver and gastrointestinal tract, inflammation, and benign tumors of the ovary and uterus (47). Normal physiological conditions may also modulate CA-125 levels because concentrations are elevated slightly during menstruation (48) and more prominently during the first trimester of pregnancy.

Use of CA-125 in Routine Patient Management. In clinical practice, CA-125 has several important roles. Elevated CA-125 in postmenopausal patients with a suspected pelvic mass raises the possibility of ovarian cancer, thus directing the patient toward a gynecological oncologist for further management. During chemotherapy, a falling CA-125 level reassures doctor and patient that the tumor is responding. A rising CA-125 level during chemotherapy can indicate development of drug resistance. This leads to an earlier change or discontinuation of ineffective therapy than if clinical criteria alone were relied on. A CA-125 level that is still elevated but falling at the end of the six courses of planned chemotherapy indicates residual disease, but it remains unclear how this should be managed. Most women in the United States have CA-125 levels measured regularly during follow-up. A rising level predicts relapse, on average, 3–4 months before there is clinical evidence of recurrence (49–52). However, there is no evidence to suggest that early treatment based on a rising level of CA-125 in an otherwise asymptomatic patient confers survival or symptom control benefits. An ongoing trial is investigating whether early reintroduction of chemotherapy impacts survival. Once relapse has been confirmed by an elevated CA-125 level, that level can be monitored to assess response to second-line, third-line, and subsequent lines of treatment. Most clinicians use serial falls between samples obtained at intervals of 3 weeks to indicate response and serial rises between samples to indicate relapse.

**POTENTIAL USES OF CA-125 IN CLINICAL TRIALS**

**Potential Use of CA-125 as a Prognostic Marker.** The potential of CA-125 as a prognostic marker has been well established, and the biomarker has some uses in clinical trials that involve large cohorts. After complete surgical removal of all ovarian cancer, the half-life of CA-125 is about 6 days, and several studies have demonstrated that those patients with a half-life of >20 days have a worse prognosis. The absolute level of CA-125 before therapy has also been shown to be of prognostic importance (51, 53–57). These factors could be used to stratify patients entering clinical trials.

The rate of fall of CA-125 predicts long-term response to therapy. For the individual patient, a serum CA-125 level of >70 units/ml measured before the third course of initial chemotherapy has been shown to be the most accurate predictor of early relapse or death (55). Moreover, the serum half-life of CA-125 during initial chemotherapy is an independent prognostic marker for survival, rate of progression, time to progression, and the chance for achieving a complete remission (49–51). A false prediction of progression rate of up to 20% limits the value of these measurements for management of individual patients. This level of error would inhibit changing the therapy of an individual patient but could be used in a clinical trial. For example, if a high proportion of patients in one arm of a randomized trial had a longer CA-125 half-life or higher CA-125 levels after three courses of therapy, this would indicate the inferiority of that line of therapy earlier than any other currently used method. Such an observation could inform an interim analysis to determine whether to discontinue this treatment arm at an early time point, thus reducing patients’ exposure to unsuccessful therapy while conserving resources (49–51, 58–61). There is an increasing need to carry out randomized trials with three to six arms; early termination of the least effective arms will benefit patients and investigators. Such an approach should be used cautiously, if any of the arms are expected to cause disease stabilization rather than partial response (see “Some Considerations for Evaluating Newer Cytostatic Drugs”).

**Potential Use of CA-125 to Calculate Response Rate to Therapy.** In addition to its potential as a prognostic indicator, CA-125 has been shown to be accurate as a tool for measuring tumor response to chemotherapy (62–70). Many more patients who are undergoing first-line treatment are evaluable according to CA-125 than those assessed by computed tomography scanning used to assess standard (WHO or RECIST) response criteria (62, 65, 71). Moreover, measurement of CA-125 is less expensive and more comfortable for patients than computed tomography scanning. In 1996, Rustin et al. (62) defined criteria for evaluating 50% and 75% response according to CA-125 (reviewed in Ref. 70 and Table 1). Using these criteria, a 50% response according to CA-125 is defined as a 50% decrease in serum CA-125 levels, as determined through a series of four CA-125 samples (two initial samples with elevated levels, the sample that shows a 50% decrease, and a confirmatory sample at the decreased level). A 75% response is established if there
Table 1 CA-125 definition of response a

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
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<tbody>
<tr>
<td>50%</td>
<td>A 50% decrease in serum CA-125 level from two initially elevated samples indicates that a 50% response has occurred. The sample showing a 50% fall must be confirmed by a fourth sample (i.e., four samples required).</td>
</tr>
<tr>
<td>75%</td>
<td>A serial decrease in CA-125 level of &gt;75% over three samples indicates that a 75% response has occurred (i.e., three samples required)</td>
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has been a serial decrease in serum CA-125 levels of >75% over three samples. In both the 50% and 75% response definitions, the final sample must be analyzed at least 28 days after the previous sample.

A recent analysis examined the accuracy of response rates obtained using 50% and 75% response definitions in predicting activity of drugs in Phase II trials for ovarian cancer, compared with response rates obtained by standard criteria (63). Data were obtained from 25 treatment groups within 19 Phase II clinical trials of 14 different cytotoxic drugs for relapsed ovarian cancer. Response rates were estimated in 1457 assessable patients according to standard criteria and in 1092 assessable patients according to CA-125. For each trial, the observed response rates acted as evaluation of how the two criteria would perform in a hypothetical Gehan two-stage Phase II trial, accepting a target drug efficacy rate of 20% and a rejection error of 5%. There was no statistical difference between response rate obtained by standard criteria and that obtained by CA-125 criteria, and therefore there was no difference in accurately predicting whether a Phase II drug is active and worth pursuing in further clinical trials. With this validated data on CA-125, its use in a clinical trial setting as a marker of response rate will have significant impact on the efficient evaluation of new drugs.

The principal outcome of any Phase II trial is to determine whether the activity of a drug is sufficient to justify continued investigation, and CA-125 measurement of tumor response has several implications for clinical trial design. For example, the decision to discontinue a clinical trial or a therapeutic regimen can be made early if the tumor response rate according to CA-125 fails to reach a predetermined threshold efficacy. Conversely, a trial that demonstrates a satisfactory response rate according to CA-125 should be expanded to include enough patients to be evaluated using both CA-125 and RECIST criteria. Interim analysis of CA-125 response rate could also be used to identify the less effective treatment arm(s) to determine which arm(s) should be discontinued. It is our belief that CA-125 response rate, using an agreed-upon definition, should be included in the protocol of all clinical trials that evaluate therapy for ovarian cancer. The definition of response based on CA-125 has been developed from extensive clinical data, and with accumulating data, a revised definition has been the subject of intensive discussion by the Gynecologic Cancer Intergroup (GCIG). Such a revision, if adopted, would involve an even simpler definition of response than that presented above.

Use of CA-125 to Evaluate Progression-Free Survival. CA-125 has been shown to be an accurate marker to define relapse of ovarian cancer (72–76). The GCIG, composed of representatives of 12 cooperative groups and the National Cancer Institute, has recently defined the date of progression according to CA-125 using Rustin’s progression criteria (77). These criteria are compared with the complementary RECIST criteria in Table 2.

We strongly recommend that CA-125 measurement be incorporated into the protocol of all ovarian cancer trials to define a date of disease progression for each patient. In addition to increasing the number of eligible patients for a given trial, measurement of disease progression by combining CA-125 measurement with standard or RECIST criteria will substantially increase the number of events in the clinical trials. In many cases, progression defined using CA-125 will be earlier than progression established using RECIST criteria. Moreover, preliminary data indicate that the CA-125-based GCIG definition is as good an indicator of disease progression as the RECIST definition when used in a variety of clinical trials for initial or relapsed ovarian cancer (72, 76). Because of the prevalence of small-volume disease in ovarian cancer, an integrated strategy that incorporates measurements of CA-125 and measurable disease will provide a more accurate representation of the total tumor burden. In certain settings, an improvement in progression-free survival using either RECIST or CA-125 criteria should be sufficient to establish clinical benefit and should be used to support accelerated approval of new drugs for ovarian cancer.

Potential Use of CA-125 as a Guide for Follow-Up in Clinical Trials. A schedule for CA-125 measurement in routine follow-up has been proposed by Vergote et al. (78). CA-125 should be monitored at each follow-up visit, ideally once every 2–3 months for the first 36 months after cessation of chemotherapy. This interval can be increased to once every 6 months for months 37–60 and once annually from 5 years after the primary diagnosis. A rising CA-125 level in an otherwise asymptomatic patient is sufficient cause for further monitoring, but not treatment by default. The decision to treat based solely on a rising CA-125 level should be based on the GCIG guidelines; doubling of CA-125 from a patient’s nadir value (or the upper limit of normal) should be the guidepost.

Some Considerations for Evaluating Newer Cytostatic Drugs. Many drugs now entering clinical trials are expected to produce disease stabilization rather than partial response. Patients with an asymptomatic rise in CA-125 levels who qualify as having progression according to CA-125 are a particularly good group in whom to test these drugs. It is important that use of an elevated CA-125 level as an entry requirement complies with the definition of progression according to CA-125 described by the GCIG (78). The classical approach to evaluating a drug would be to then randomize patients between a test therapy and control or no treatment. Obtaining definitive data in such a study requires hundreds of patients, so there is a need to develop models for assessment in far fewer patients.

There are several potential options as to how efficacy could be ascertained according to CA-125. The simplest is to use the
Table 2 Comparison of RECIST* and GCIG definitions of progression-free survival for patients in first-line therapy for ovarian cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patient category A*</th>
<th>Patient category B</th>
<th>Patient category C</th>
<th>Date of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCIG (CA-125)</td>
<td>CA-125 &gt; 2× ULN documented on two occasions</td>
<td>CA-125 &gt; 2× nadir value on two occasions</td>
<td>As for patient category A</td>
<td>Patient categories A and C: first date of CA-125 elevation ≥ 2× ULN</td>
</tr>
<tr>
<td>RECIST (measure evaluable disease)</td>
<td>Any new lesions (measurable or nonmeasurable) or a 20% increase in sum of longest diameters compared with baseline (or lowest sum while on study if less than baseline)</td>
<td></td>
<td></td>
<td>Patient category B: first date of CA-125 elevation ≥ 2× nadir</td>
</tr>
</tbody>
</table>

*REClST, Response Evaluation Criteria in Solid Tumors; GCIG, Gynecologic Cancer Intergroup; ULN, upper limit of normal.

* Patient category A, patients with elevated CA-125 levels pretreatment that normalize on first-line chemotherapy; Patient category B, patients with elevated CA-125 levels pretreatment that fail to normalize on first-line chemotherapy; Patient category C, patients with normal pretreatment CA-125 levels.

response criteria discussed above. If only disease stabilization is expected, one could look for falls of <50% that are maintained for a specified period as performed in a trial of isotretinoin and calcitriol (79). If patients are having CA-125 measurements for a specified period as performed in a trial of isotretinoin and calcitriol (79). If patients are having CA-125 measurements every 2–3 months during follow-up, the time from last CA-125 level within the normal range to a level twice the upper limit of normal can be used to calculate the doubling time off therapy. This value can then be compared with the doubling time after starting a new therapy. Data from the delayed treatment arm of the Medical Research Council/European Organization for Research and Treatment of Cancer CA-125 follow-up will clearly demonstrate the slope of the CA-125 rise over time in >150 patients. These data will show the linearity of the CA-125 rise and the potential reliability of comparing slopes before and after introduction of a novel agent. If this use of CA-125 can indicate efficacy for cytostatic drugs in a Phase II setting, it could be used to select those drugs meriting evaluation in far larger randomized trials.

Another option would be to consider the CA-125 level at the start of the new trial therapy as the “nadir” CA-125 level. A confirmed doubling from that level would then be considered progression. The time before progression could be considered the period equivalent to stable disease.

Any unrecognized CA-125 definition such as stable disease would require precise definition. It would then require testing in different trials and validation against standard criteria. If just a doubling of CA-125 levels is used as an entry requirement, the CA-125 level might not continue to rise at the same rate (80). Consequently, serial monitoring of CA-125 will be required to accurately identify a change point where the rise in CA-125 is significantly altered (slowed). In this regard, mathematical analysis similar to that used for early detection of ovarian cancer with serial CA-125 values must be developed (81). A cautious approach such as serial monitoring is therefore necessary when introducing any new definitions based on CA-125.

Incorporation of Defined Evaluation Criteria into Ongoing and Contemplated Phase II and Phase III Trials Evaluating New Drugs/Regimens for Treatment of Ovarian Cancer. There are a large number of ongoing Phase II and Phase III clinical trials evaluating new uses and regimens of approved drugs, as well as new cytotoxic and cytostatic drugs for treatment of ovarian cancer. The reader is referred to a representative sample of these ongoing trials, and some of these trials have incorporated the Rustin CA-125 response rate criteria as well as the GCIG criteria for definition of progression-free survival herein described (77). Whereas much specific detail is required to describe ongoing or contemplated trial designs, provision in schematic form of a prototype Phase II trial using these criteria (Fig. 1) demonstrates the general applicability and value of these methods for making progress in development of drugs for treatment of ovarian cancer.

**SUMMARY AND RECOMMENDATIONS FOR USE OF CA-125 IN EVALUATION OF ONCOLOGIC DRUGS FOR OVARIAN CANCER**

There is currently a wealth of data to support the acceptance of CA-125 as a marker in clinical trials for the evaluation of oncologic drugs for ovarian cancer (82). It is our belief that CA-125 has numerous applications in the design of clinical trials, from prognosis to follow-up. Acceptance of CA-125 level as a biomarker for ovarian cancer will double the number of patients eligible for clinical trials in ovarian cancer. CA-125 should be viewed as a tool that is complementary to standard criteria for disease measurement. By combining CA-125 measurement with RECIST criteria, therapies can be evaluated more rapidly, and unsuccessful therapies can be discontinued. These applications will benefit both the patient and the investigator.

Trial data that demonstrate the utility of a drug based on progression-free survival according to validated CA-125 and RECIST criteria proposed by the GCIG should be used to support accelerated approval of promising therapies. We therefore propose the following recommendations with respect to CA-125 in clinical trials for ovarian cancer.

(a) CA-125 should be used routinely in Phase II clinical trials to support “go/no go” decisions for further development.

(b) Trials to determine response rates using both CA-125
criteria and RECIST criteria would be designed so that if the CA-125 response rate is greater than a figure that has 90% power to detect the minimal acceptable rate, the trial would be continued so that response can be measured with the same power by RECIST criteria.

(c) It should be appreciated that in trials of initial chemotherapy early CA-125 response is to both surgery and chemotherapy; thus, these values should not be recorded as response to chemotherapy. Because the CA-125 half-life is 1–2 weeks, the CA-125 response to surgery should no longer be a factor by the start of the third course of treatment. Therefore, treatment arms of multiarm trials of initial therapy should record the proportion of patients with either CA-125 levels >2× the upper limit of normal at the start of their third course of chemotherapy (6–8 weeks from start) or CA-125 half-lives of >20 days. Consideration should be given for early discontinuation of those arms with significantly inferior prognosis defined by CA-125.

(d) Progression-free survival and, specifically, the date of progression should be defined according to the CA-125 and RECIST criteria proposed by the GCIG.

(e) CA-125 should be considered in Phase I and II trials to identify the biologically optimal dose and cytostatic activity of nonconventional therapies such as signal transduction inhibitors. Several methods for establishing and evaluating response criteria for these newer cytostatic drugs are discussed, and their validation is and should be the subject of ongoing and new trials.

(f) Newer technologies such as proteomics and functional imaging should greatly aid cohort selection for both Phase II and pivotal trials and could eventually be valuable adjunctive end points to CA-125 in evaluating new ovarian cancer therapies. Furthermore, proteomic analysis may be able to identify protein markers correlating to therapeutic response for which CA-125-like assays could be developed. These assays could complement CA-125.

(g) With new therapies, trial data that demonstrate CA-125 response (as defined here and in previous publications) and an improvement in progression-free survival defined according to the CA-125 and RECIST criteria proposed by the GCIG should be used to support accelerated approval of promising therapies. These trials would be designed to allow continuation of evaluation to survival or quality of life end points or to be followed in Phase IV confirmatory trials using these standard end points.

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