The Role of CA-125 in the Management of Ovarian Cancer

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ABSTRACT

Over more than a decade of clinical use, CA-125 has proven itself to be one of the most useful tumor markers in cancer medicine. The major clinical utility of this serum marker is in following the clinical course of women with known ovarian cancer. Other potential uses of CA-125 include the evaluation of the effectiveness of new antineoplastic agents in this malignancy, and in the modification of treatment strategies in individuals whose CA-125 levels fail to decline at an acceptable rate following the institution of therapy. At the present time, the use of CA-125 as a method to screen for ovarian cancer should be considered investigational.

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INTRODUCTION

The serum level of CA-125, a mucin-like glycoprotein of molecular weight >200,000 [1], has been demonstrated in multiple clinical trials and standard oncologic practice to be one of the most useful tumor markers in cancer medicine [2, 3]. In this review the established and potential uses of CA-125 in the management of ovarian cancer will be discussed, along with concerns for the overuse, or actual misuse, of this valuable clinical test.

CLINICAL SETTINGS WHERE THE CLINICAL UTILITY OF CA-125 HAS BEEN ESTABLISHED

The most common use of CA-125 is in following the clinical course of patients with documented ovarian cancer where the disease is not easily measurable or evaluable by other means. Following standard surgical debulking, a significant percentage of patients with ovarian cancer will persist with having only small-volume or microscopic residual intra-abdominal disease. Even with larger tumor volumes remaining after surgery, symptoms may be absent and physical findings or radiographic evaluation may not be helpful in documenting a response of the cancer to cytotoxic chemotherapy.

In addition, symptomatic patients or those with measurable or evaluable disease (e.g., ascites) who respond to treatment may eventually become “non-evaluable” for further evidence of a response. In each of these clinical settings, the serum level of CA-125 can provide helpful information regarding the initial response or continued response to later courses of chemotherapy. The percentage decrease in CA-125 which should be considered a “response” to therapy is a matter of some discussion in the oncologic literature. In a recent editorial, this author has proposed two “CA-125 response criteria” which could be employed in examining new antineoplastic drugs or strategies in ovarian cancer [4]. The proposed “criteria” are a ≥50% or ≥90% decrease in the CA-125 antigen level, compared to baseline (i.e., value obtained just prior to the initiation of the specific therapeutic program). Rustin et al. examined a large retrospective database of ovarian cancer patients to develop a model whereby the percentage decrease in CA-125 could closely coincide with the objective response rate as predicted by “response of measurable disease” [5]. This analysis led to the proposal that either a 50% decrease after two samples (compared to baseline), confirmed by an additional sample, or a 75% decline observed over three samples, be accepted as a responding patient. Individuals’ samples are to be separated in time by a minimum of 28 days.

For patients being treated on a clinical trial, specific criteria for “response” are generally built into the study design, along with indications to continue or stop treatment. However, for the majority of ovarian cancer patients who are not entered into investigative studies, is there a specific percentage decrease in CA-125 antigen level which should be considered a “response” to treatment?

In the absence of specific data from clinical trials, it is difficult to provide a definitive answer to this question. However, in the opinion of this author, if a patient has an elevated CA-125 level at the initiation of chemotherapy
which, at that point in time, is at least double the upper range of normal (i.e., >60 U/ml), it is reasonable to consider a 50% decrease from baseline (in the absence of any indications of clinical tumor progression) to indicate an anti-tumor effect. Larger percentage decreases and more rapid falls in the antigen level indicate greater tumor cell kill.

It must be remembered that this tumor marker (like all other tumor markers) should not be employed in isolation, or independent of the specific clinical setting. For example, if the CA-125 antigen level decreases but the patient has clinical evidence of disease progression (e.g., development of ascites, increased mass on pelvic examination), the marker value has little importance.

As with all laboratory tests it is also possible that the test value returned to the physician is actually that of no other patient, that there may have been a technical problem within the laboratory causing an error, or that there may have been a transcription mistake when the test results were recorded. Thus, in general, decisions regarding patient management should not be based on the results of a single CA-125 test unless there are supporting data (e.g., physical findings, symptoms) for the serum antigen level.

Just as a CA-125 value is a reasonable indicator of response, a rising level can be employed as one indication of the failure of a particular therapy [6]. Again, one must be careful when using this tumor marker to indicate the lack of benefit from treatment, particularly with initial chemotherapy, in view of the important prognostic implications of this conclusion.

However, when it is confirmed that the CA-125 level is rising, despite therapy, it is appropriate to question the value of subjecting a patient to the toxicity of a treatment program in the absence of clinical benefit.

The percentage increase in CA-125 levels which should be accepted as evidence of disease progression has not been agreed upon in the oncologic literature. However, in clinical practice it would appear reasonable to accept a confirmed (at least two samples) doubling of the CA-125 from a baseline value (with a minimum baseline at the upper limit of normal for the laboratory, usually 35 U/ml) as an indication of disease progression. Lesser degrees of change in the CA-125 value may indicate lack of response (so-called “stable disease”) but should probably not be considered as actual disease progression in the absence of supporting data (e.g., new ascites, presence of a new mass on physical examination).

The CA-125 antigen level has also proven to be useful in demonstrating the persistence of disease following the completion of a standard chemotherapy regimen (e.g., 6 cycles of cisplatin/paclitaxel). If the CA-125 level remains abnormal, there is a >95% certainty that residual disease is present [7]. Even if a second-look surgery were performed and failed to confirm persistence of disease, it is likely that the elevated value reflects the presence of either microscopic cancer undetected within the peritoneal cavity or extra-peritoneal disease.

Unfortunately, it is well-established that the opposite situation is not true. That is, a normal CA-125 value at the completion of chemotherapy does not indicate the absence of disease. Several studies have reported that approximately 50% of patients with advanced ovarian cancer whose CA-125 levels return into the normal range will have persistent microscopic or macroscopic disease at second-look surgery [8-10].

Finally, a rising CA-125 level in patients with ovarian cancer whose CA-125 level had previously entered the normal range usually indicates disease progression [11]. However, as previously noted, a single elevation of the CA-125 in the absence of confirmatory data (e.g., new symptoms, physical findings) should not be accepted as definitive evidence of disease recurrence. While other causes of an elevated CA-125 are always possible (e.g., intra-abdominal infection, liver dysfunction, the development of a new primary cancer) [12], in the vast majority of cases a confirmed rise (at least two values) indicates return of the disease.

**Potential Uses of CA-125**

As previously noted, a CA-125 response can be potentially utilized in trials of new anticancer agents [4]. Currently, patients without “measurable disease” are excluded from most phase II clinical trials of investigational drugs or strategies. This state of affairs often denies such patients access to new agents.

In addition, treating patients with only measurable disease imposes a particularly difficult task on these experimental drugs, as patients with measurable disease usually have considerably more tumor bulk than patients who do not have measurable masses. By employing CA-125 as a marker for disease response or progression, new drugs may be more rapidly screened for antitumor activity, and their effectiveness against small tumor volumes may be evaluated.

However, the clinical validity of this hypothesis must be directly tested in trials employing CA-125 as a surrogate marker for decrease in measurable tumor masses before it can be routinely considered as an acceptable marker in studies in ovarian cancer.

The initial level of CA-125 [13, 14] and the rate of decline following the institution of chemotherapy [15-20] have been suggested to be of important prognostic significance in ovarian cancer. In general, patients with extremely elevated values have greater tumor bulk than individuals with lower abnormal levels. Similarly, it is reasonable to state that patients whose CA-125 values fall rapidly following the initiation of chemotherapy are likely to be experiencing greater degrees of tumor cell kill and have cancers more sensitive to the cytotoxic agents employed compared with individuals exhibiting slow rates of decline in this marker level.
As a result, it might be proposed that patients presenting with very high (e.g., >2,000 U/ml) CA-125 antigen levels or those exhibiting “slower” rates of decline be treated with alternative treatment approaches compared to “standard therapy” of ovarian cancer. Such a management strategy has been considered utilizing the level of B-HCG (beta human chorionic gonadotropin) in advanced testicular cancer [21].

Unfortunately, at the present time, there is no evidence in ovarian cancer that employing alternative initial chemotherapy regimens (e.g., high-dose chemotherapy with marrow or peripheral progenitor cell rescue) can improve the ultimate clinical outcome of the malignancy. Thus, while the use of CA-125 for this indication is attractive, it must be considered highly investigative at the present time.

**Potential “Overuse” of CA-125**

As noted, a rising CA-125 antigen level generally indicates disease recurrence in a patient who has previously normalized her level, even in the absence of signs or symptoms of disease. However, to date, there are no data available to demonstrate that this information is of any direct clinical relevance. Stated differently, there is no evidence that re-institution of therapy in an asymptomatic ovarian cancer patient with a rising CA-125 antigen level improves either survival or quality of life, compared with simply waiting until there are clinical signs or symptoms of disease progression.

In fact, it can be reasonably argued that restarting chemotherapy at an earlier time point may actually decrease the overall quality of life compared with treating only when symptoms develop [22]. The clinical utility of a strategy of “early re-institution” of chemotherapy must be evaluated in a well-designed controlled phase III randomized trial comparing this approach to treatment only after patients develop signs or symptoms of disease recurrence [23].

Concern can also be raised with the often “standard practice” of obtaining a CA-125 level to “reassure a patient” that her disease remains “in remission.” As stated previously, a normal CA-125 value provides little if any reassurance regarding the absence of disease activity. Only prolonged (i.e., many years) follow-up can provide any assurance the ovarian cancer will not recur in patients initially presenting with advanced disease.

**Potential Misuse of CA-125**

Data currently available indicate CA-125 is not a useful test for screening for ovarian cancer and that this laboratory test should not be used for this purpose outside carefully controlled clinical trials. Justification for this strong statement includes:

1. At least 50% of patients with documented stage I ovarian cancer will not have an elevation in CA-125. Thus, this marker will never be of any benefit in 50% of patients with “early-stage disease.”

2. CA-125 is not a specific marker for ovarian cancer, as it is elevated in a number of other tumor types [12, 14-26], including cancer of the breast and gastrointestinal malignancies.

3. CA-125 is not even specific for cancer, being abnormal in a variety of benign conditions affecting women [12, 27-29], including endometriosis, pelvic inflammatory disease, alcoholic cirrhosis, and infectious peritonitis.

4. Finding an abnormal CA-125 level in the absence of other signs or symptoms of ovarian cancer (e.g., adnexal mass) frequently leads to extensive investigative efforts and unnecessary surgery (e.g., laparoscopy or laparotomy for benign conditions) with the potential for morbidity or even mortality. Further, the finding of an “abnormal CA-125 level” can lead to the development of considerable and prolonged anxiety for the individual, as well as for her family and physician.

5. At the present time, there is no evidence that detecting ovarian cancer as a result of finding an isolated CA-125 elevation impacts favorably on ultimate survival. The few patients reported to have been “discovered” to have “early-stage disease” may simply reflect the long natural history of ovarian cancer in some patients, as currently >10% of all patients with ovarian cancer will be found at the time of surgical staging to have stage I disease without having undergone CA-125 screening.

In summary, screening for ovarian cancer with tumor markers (including CA-125) or other methods (e.g., vaginal ultrasound) remains an investigative strategy [30-35]. There is currently no evidence that such an approach should be employed routinely outside the clinical trials setting.

It is reasonable to suggest that individuals at particularly high risk for the development of ovarian cancer (e.g., strong family history, BRCA-1 positive) may experience some benefit from a screening program which might include the use of CA-125. However, as noted above, the clinical utility of such a strategy must be subjected to examination in well-designed clinical trials.

**Conclusion**

It has been >15 years since Bast and Knapp described the CA-125 antigen and proposed its potential use as a diagnostic tool in ovarian cancer [1, 2]. Since that time, CA-125 has proven itself to be a valuable addition to the oncologist’s armamentarium when managing women with this malignancy. Further investigative efforts are required to determine how this marker may be rationally and optimally employed in new drug development and treatment of patients with persistent or recurrent disease following initial cytotoxic chemotherapy.
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