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Commentary: CA125 and the detection of recurrent ovarian cancer: A reasonably accurate biomarker for a difficult disease

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Since the first description of the assay by our group more than 25 years ago,1 measurement of serum CA125 has contributed to the care of patients with ovarian cancer in several different ways. The original application of CA125 was in monitoring response of ovarian cancer during chemotherapy and in detecting persistent disease following primary treatment.2 In patients whose cancers shed sufficient quantities of CA125 to be elevated in peripheral blood, biomarker levels have tracked tumor volume with up to 90% accuracy.3 After cytoreductive surgery and combination chemotherapy, persistent elevation of CA125 levels has correlated with persistent disease in >90% of cases.2،3 CA125 is not, however, optimally sensitive and up to 50% of patients with normal levels of CA125 following chemotherapy were found to have small volumes of persistent disease at second look operations.2،3

At the time of diagnosis, elevated CA125 has been combined with ultrasonography4 and other biomarkers5،6،7 to identify those patients with pelvic masses who are most likely to have ovarian cancer and who would benefit from referral to a gynecologic oncologist for primary surgery. Perhaps the most promising application of serial CA125 determinations is to identify a small fraction of healthy postmenopausal women who would benefit from transvaginal sonography to detect ovarian cancer at an early stage.8 Early results from the UKCTOCS trial involving 200,000 women in the United Kingdom suggest that rising CA 125 followed by transvaginal sonography can nearly double the fraction of cancers detected in early stage and require no more than 3 operations for each case of ovarian cancer detected.8 A SPORE sponsored trial in the United States has confirmed these observations, albeit on a much smaller scale.9 The UKCTOCS trial is adequately powered to detect a survival advantage and results will be available in the next 2-3 years.

CA125 has also been used over the years to detect recurrence of ovarian cancer after primary therapy. More than half of women treated for advanced disease with cytoreductive surgery and combination chemotherapy will experience a complete clinical response with normalization of CA125 and without evidence of gross disease on imaging studies. If “second look” operations are performed, more than half of patients in “clinical remission” will have macroscopic or microscopic metastases that fall beneath the limits of resolution for imaging and the sensitivity of CA125. Even when second look procedures are negative, the majority of patients will experience recurrence of disease within months to years. Increasing levels of CA125 precede the signs and symptoms of recurrence by 3-5 months in as many as 70% of cases.10،11 The practice in the United States has been to monitor CA125 every three months during the first years following primary treatment, on the assumption that detection of recurrence would translate into more effective treatment of small volume disease.

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A recent study, presented as a plenary paper by Dr. Gordon Rustin at the 2009 ASCO meeting, has questioned the value of monitoring patients for disease recurrence with CA125.12 In this trial, patients presumed to be in complete remission after primary therapy had CA125 determinations every three months, but were blinded to the results. When CA125 values doubled outside the normal range, patients were randomized to have or not to have their physicians informed of the rising value. Some 265 patients in the “early” group were treated at the discretion of the participating physicians with second and sometimes with third line chemotherapy. Another 264 patients in the “delayed” group were treated with second line chemotherapy when their recurrent disease became symptomatic or clinically obvious, some 4.8 months later than the “early” group where treatment had been based on CA125. The study accrued slowly and required more than 9 years to complete, but in the final analysis no difference was observed in overall survival nor any improvement found in quality of life by earlier detection of recurrent disease. The quality of life deteriorated in both groups, but this occurred 2.6 months sooner in the group treated “early”, related primarily to the side effects of chemotherapy, particularly fatigue. CA125 had accurately predicted disease recurrence, but earlier treatment had not impacted significantly on clinical outcome and had slightly, but significantly, hastened a decline in quality of life.

Rustin and colleagues should be congratulated for their persistence and organizational skill in carrying out a study in multiple institutions over nearly a decade. Their trial addresses an important problem and challenges the status quo. Physicians in the UK and in the United States have been appropriately concerned by the anxiety surrounding each CA125 determination in a fraction of patients.13 Small increases in CA125 can also prompt negative imaging studies with their associated inconvenience and expense. In addition, CA125 can rise persistently in the absence of abnormalities on imaging or physical examination, posing the therapeutic dilemma of whether and how to treat a rising CA125. Based on the recent ASCO report, the UK investigators have argued that there is no value in the routine measurement of CA125 in the follow-up of ovarian cancer patients who attain a complete response after first line treatment and that practice should change.

Since initiation of Rustin's UK trial in 1996, both the use of CA125 and the standards for chemotherapy of recurrent disease have, however, evolved. Before we change practice and abandon monitoring for recurrence of ovarian cancer based on a single negative study, it will be important to consider the limitations of the trial, as well as the rationale for treating recurrent ovarian cancer at an early interval.

While the “early” and “delayed” arms of the trial are well balanced for many relevant prognostic variables, there are several technical problems with the trial design that may have led inadvertently to an imbalance of the arms. Patients were not stratified for the degree of primary cytoreduction or for tumor grade. Trial participants were restaged following primary surgery and chemotherapy with CA125 and imaging, but the modalities and criteria for imaging were not standardized. Even with imaging by CT scans, at least half of patients with a normal CA125 will have gross residual disease at second look surgery and this is more likely in the context of suboptimal initial cytoreduction. Randomization of more patients with suboptimal cytoreduction, high grade cancers and macroscopic residual disease after treatment to the “early” arm could well have nullified a modest improvement in overall survival.

Of greater concern is that CA125 had to double outside the normal range before physicians were informed of potential disease recurrence. At the time the study was planned, this was a reasonable benchmark and produced almost 5 months of lead time. We now know that increases of CA125 within the normal range of 35 units per ml can precede disease recurrence with an even greater lead time.14,15

In addition, physicians were simply informed that CA125 was rising and each physician was free to choose whether to treat, when to treat and what drugs to use. Randomization was completed within one month after the CA125 determination. While 50% of patients began chemotherapy within the first month after randomization, three months were required for 90% to initiate second line chemotherapy and 4% on the “early” arm of the trial never received treatment. With only 4.8 months of lead time, treatment of half of patients was unacceptably delayed.

Of critical importance, only one third of patients received a combination of carboplatin and taxane; two thirds received single agent therapy or a combination that lacked a taxane. The ICON 4/AGO trial was completed in the UK during the same years as Dr. Rustin's study and demonstrated that a combination of carboplatin and paclitaxel produced significantly longer progression free and overall survival than did treatment with carboplatin alone as a single agent.16 Consequently, one half of patients on the “early” arm were treated late and two thirds received suboptimal treatment by today's standards. If these factors are independently assorted, only 16% of patients would have been treated promptly with optimal chemotherapy and could have benefited from early detection of recurrence.

In this trial, CA125 accurately predicted disease recurrence. An apparent failure to impact on survival related to the inadequacy of therapy for recurrent disease. In the future, how are we to improve treatment for recurrent and for primary ovarian cancer? On average, women with ovarian cancer survive only 12-18 months after clinically apparent disease recurrence, but there is a small fraction of women who survive up to a decade after responding to multiple drugs, individually and in combination. Currently, there are at least seven conventional drugs available to treat recurrent ovarian cancer, producing an objective response rate. In the absence of an effective predictive test, oncologists generally prescribe single drugs or two drug combinations sequentially, requiring 2 – 3 months to determine the response to each regimen. Waiting for recurrent disease to grow to a point where it causes symptoms or can be readily palpated will shorten the interval available to test these conventional agents and to give patients an opportunity to benefit.

As important, the CA125 trial underlines the critical need to improve treatment of recurrent ovarian cancer. At present, there are more than 400 new drugs being developed to treat different forms of cancer. Almost certainly, combinations of these agents will be required for optimal benefit. At present, only 4% of Americans with cancer participate in clinical trials. For ovarian cancer, the fraction may be even lower in that a smaller number of patients meet RECIST criteria. By unnecessarily delaying detection of recurrence, we are likely to further decrease participation in clinical trials, as women will have fewer months with adequate performance status.

Rustin's trial does mandate that oncologists discuss with each patient whether or not she wishes to have her disease monitored for recurrence with CA125. If a patient did not want to be treated with multiple or novel agents at the time of disease recurrence, she could be reassured that early detection of recurrence would not translate into longer life. If, however, a patient would wish to receive multiple conventional drugs or to consider participating in clinical trials, monitoring CA125 would provide additional months for treatment.

In a cost conscious health care environment, one possible outcome of the study reported at ASCO would be for Medicare and other third party payers to deny coverage for monitoring disease recurrence with CA125 or other biomarkers regardless of the wishes of patients or physicians. This would be unfortunate, as it would be based on a single limited study, would ignore progress in monitoring and therapy since 1996 and would assume that there will be no further improvement over the next several years.

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