Follow-up with CA125 after primary therapy of advanced ovarian cancer has major implications for treatment outcome and trial performances and should not be routinely performed

G. J. S. Rustin*
Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK

Background: Only one randomized trial has examined the value of performing routine CA125 measurements during follow-up of ovarian cancer. The results of this trial and implications of frequent CA125 measurements are examined.

Patients and methods: The Medical Research Council OV05/European Organisation for Research and Treatment of Cancer 55955 trial enrolled 1442 patients with a CA125 level within the normal range following platinum-based chemotherapy for epithelial ovarian cancer. If CA125 levels rose to more than twice the upper limit of normal, patients were randomized to immediate or delayed chemotherapy.

Results: Those randomized in the early arm started chemotherapy a median of 4.8 months earlier than those on the delayed arm. There was no difference in survival between the early and delayed arms.

Conclusions: Women should be advised not to have routine CA125 measurements, providing they are well and have no symptoms suggesting relapse. In asymptomatic patients with a rising CA125 level, chemotherapy can be delayed. Earlier stopping of maintenance therapy just because of rising CA125 might deny patients continuing benefit from that therapy. Use of CA125 to define progression could result in platinum-sensitive patients being falsely classified as platinum resistant.

Key words: CA125, ovarian cancer, follow-up, tumour progression, relapse

introduction
It has become standard practice around the world to perform routine CA125 measurements on women who have completed chemotherapy for ovarian cancer. The main reason for follow-up given by German ovarian cancer patients was that they thought it would lead to them living longer [1]. It is a poor reflection on the medical community that patients have been led to believe an important concept for which there is no evidence. It is obvious that if earlier detection of relapse leads to improved outcome, then the earlier the relapse is detected the better. However, if earlier detection does not improve outcome, an earlier diagnosis of relapse leads to patients living longer with the knowledge that their cancer is relapsing yet deriving no benefit from this knowledge.

This article explains the results and implications of the only randomized trial that has compared early versus delayed treatment for relapsed ovarian cancer, providing for the first time the evidence that will allow follow-up policies to be appropriately developed. What is perhaps not appreciated is how different follow-up policies can influence not only the timing of treatment for relapse but also the duration of maintenance therapy. Different follow-up schedules can also influence the date of progression, which is a major endpoint in clinical trials. I will show how, using the latest research results, a sensible follow-up schedule can be applied [2].

the MRC OV05/EORTC 55955 trial
A woman with a rising CA125 concentration, who remains well, without symptoms or signs of recurrent disease, presents a major management dilemma. To resolve this dilemma, a trial was designed to compare early treatment of relapse based on a rising CA125 level with delaying chemotherapy until signs or symptoms of relapse [3]. The Medical Research Council (MRC) OV05/European Organisation for Research and Treatment of Cancer (EORTC) 55955 trial enrolled 1442 patients who had a complete remission with a CA125 level within the normal range following platinum-based chemotherapy for epithelial ovarian cancer. They had follow-up consultations and blood taken for CA125 measurement every 3 months. The results were blinded from both the clinicians and patients, and were sent to the MRC or EORTC trials centres. If the levels rose to more
Patients in the early arm were an earlier deterioration in the quality of life of those who received more lines of chemotherapy. Not surprisingly, there was no difference in survival to those in the delayed arm, they must in total have received more lines of chemotherapy a median of 4.6 months earlier than those in the delayed arm [HR: median, 0.69 (95% confidence interval, 0.58–0.83); delayed arm: median, 27.1 months (95% CI, 22.8–30.9); hazard ratio (HR); median, 0.98 (95% CI, 0.80–1.20); P = 0.85] (Figure 1). Furthermore, third-line chemotherapy was started in those in the immediate arm 4.6 months earlier than in those in the delayed arm [HR: median, 0.69 (95% CI, 0.58–0.83); P = 0.0001]. Although data were not collected for therapy after third-line chemotherapy, it is likely that later lines of chemotherapy were also started earlier in those in the early arm. As those in the early arm had similar survival to those in the delayed arm, they must in total have received more lines of chemotherapy. Not surprisingly, there was an earlier deterioration in the quality of life of those patients in the early arm.

**Implications for clinical practice**

For the first time, women can be given evidence to help them decide how they wish to be followed up after receiving first-line chemotherapy. They can decide:

- Not to have routine CA125 measurements providing they are well and have no symptoms suggesting relapse.
- To continue having CA125 measurements, but not be told the results. This option is particularly useful if they are in a clinical trial where routine CA125 measurements are mandated, but reduces anxiety over waiting for the result.
- To have routine CA125 measurements, so that they have more warning as to when they might require relapse chemotherapy.

In patients whose CA125 is rising but who remain asymptomatic, the OV05/55955 trial clearly shows there is no need to restart chemotherapy until symptoms develop. A computed tomography (CT) scan that shows minimal or no disease can help patients to delay chemotherapy.

It is only possible for patients to make sensible choices regarding follow-up if they are given adequate information. It is advisable to routinely discuss the rationale of follow-up with patients when they complete first-line chemotherapy for advanced ovarian cancer. If they are in complete remission with a normal CA125 level (the entry criteria for OV05/55955) they can be told that they have almost a 50% chance of surviving 6 years, from completion of their first-line chemotherapy. They need to know that there is a high chance of relapse, but also a good chance of benefit from further chemotherapy. My perception from debating this topic around the world is that those patients who are told by their doctors that relapsed disease can be treated but not cured are more likely to accept the results of OV05/55955 and not have routine CA125 measurements performed. Those doctors who are happy that their patients believe that cure of relapsed ovarian cancer is still possible find it difficult to persuade their patients not to have routine CA125 measurements. Obviously, if there was a reasonable chance of cure then we would all wish to treat as early as possible.

There are further requirements to enable safe follow-up of ovarian cancer patients who opt for no routine CA125 measurements. They need to be told what symptoms should prompt an early clinic appointment. A list of likely symptoms can be supplied. It is essential that there are facilities for patients to make urgent appointments. Easy availability of a support nurse for telephone advice can be a great help.

Some surgeons remain convinced that they can improve the survival of selected patients with relapsed ovarian cancer and that the earlier the relapse is detected the better the chance of optimal surgery. A recent small study showed that those patients whose surgery was prompted by a rising CA125 level had a worse survival than those whose relapse was detected by symptoms or routine examinations and scans [4]. Hopefully, the DESKTOP 3 and GOG 213 trials will provide randomized trial data to demonstrate whether there is a survival benefit from surgery for relapse. Surgery is only of value if it can result in complete macroscopic removal of recurrent cancer. There is therefore no point in doing routine CA125 measurements in those patients who are not candidates for surgery, which is most patients during the first 12 months following first-line therapy. Data from DESKTOP 1 and 2 suggest this also includes all patients who had residual disease after initial surgery, performance score >0 and presence of ascites [5].
implications for research

As mentioned above, it is still reasonable to do routine CA125 measurements as part of clinical trials, but patients should be offered the chance of not having their results divulged if they are well. This decision must be clearly recorded in the patient’s notes, so that all those seeing this patient are aware of her decision. Patients with an asymptomatic rise in CA125 are an ideal group to test minimally toxic agents, such as tamoxifen, that might slow tumour progression [6]. If such trials are available locally, patients should be given information about them as they might then wish to have regular CA125 measurements, so that they can enter a trial where an entry criterion is a rising CA125 level. The ideal group of patients are those who have already relapsed and responded to their relapse therapy. These patients know they will relapse again and are keen to enter trials that might delay their next relapse. A trial is underway in which patients start tamoxifen once their CA125 levels have reached four times the nadir level (http://clinicaltrials.gov/show/NCT00305838). It is postulated that the slope of the rising CA125 levels before starting an active agent should be greater than after starting the agent. It is hoped that fewer patients would be required to show that a drug can significantly prolong the doubling time of CA125 than would be required in a randomized trial.

Progression-free survival is increasingly used as an endpoint in clinical trials. Now we know that early treatment of relapse provides no survival benefit, we need to address how patients should be managed if they have progressed just according to CA125. All trials should now give patients the choice of not knowing their CA125 measurements. Where patients are on maintenance therapy, providing it is well tolerated they should be allowed to continue until either a defined timepoint or until symptomatic progression. This is particularly important for drugs such as bevacizumab, which has been shown to delay progression-free survival [7, 8]. The definition of progression, either by RECIST or CA125, indicates progression when precise criteria such as a 20% increase in tumour dimension or 50% increase in CA125 level have been reached. An agent that is delaying that event might well still be working at the date of designated progression and if continued could further delay symptomatic progression.

A good case could therefore be made for not doing regular CT scans and CA125 levels during maintenance therapy, as they could harm patients by leading to the premature stopping of an active agent.

The OV05/55955 trial shows that patients having 3-monthly CA125 measurements during follow-up have CA125-defined progression 4.8 months earlier than those not having routine CA125 measurements. This has major implications if the time from last platinum chemotherapy to relapse is used to define platinum resistance. Thus, a patient who has CA125-defined progression at 4 months might well not develop symptoms and then have RECIST-defined progression until 8 or 9 months following their last platinum therapy (Figure 2).

Figure 2. Example of treating a patient because of their CA125 rising to above the upper limit of normal (ULN) (point B), when they are 4 months from completion of their last platinum chemotherapy and considered platinum resistant, or waiting until they develop symptoms at 8 months (point A) and are considered platinum sensitive. It also shows that more cycles of chemotherapy are given if chemotherapy is started just because of an elevated CA125.

meeting of the Gynecologic Cancer InterGroup tried to resolve this issue by insisting that it should be stated for each patient whether the relapse was detected first by RECIST or CA125 and whether symptoms were present. Trial protocols could then specify whether asymptomatic patients with an elevated CA125 level are eligible.

conclusion

The lack of benefit from earlier treatment with its deleterious effect on quality of life should lead everyone to question whether they should alter their follow-up practice. It is a fact of life that many people will find any excuse to resist change. Some doctors will find aspects of the OV05/55955 trial unsatisfactory; however, none of the published criticisms are serious enough to undermine the main conclusions of the trial [9–11]. Some will say that patients insist on having regular blood tests. Some patients will, but in my practice, following information about OV05/55955 results and adequate counselling, the great majority now prefer not to have routine CA125 measurements.

disclosures

The author has declared no conflicts of interest.

references


