Follow-up with CA125 after primary therapy of advanced ovarian cancer: in favor of continuing to prescribe CA125 during follow-up

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Serum cancer antigen 125 (CA125) is widely used in ovarian cancer to monitor the effectiveness of therapy both in first line and recurrence. It is also widely used during follow-up, where it is able to identify a percentage of patients with asymptomatic recurrence. Although a recent Medical Research Council (UK)/European Organisation for Research and Treatment of Cancer trial has demonstrated that early chemotherapy in asymptomatic patients based only on CA125 increase does not prolong survival, we still believe that CA125 monitoring should be prescribed to patients during follow-up. In fact, it can help to identify patients who should undergo radiology in order to select those that can benefit from surgery or from early treatment before the onset of symptoms, which are usually related to an excessive disease burden. The delay of disease symptoms, such as those associated with the appearance of ascites or bowel occlusion, is in our view an important goal of our treatment of recurrence. Moreover, research should be done in patients with asymptomatic CA125 increase in order to identify more effective therapies that will improve survival. Finally, the reliability of CA125 as a surrogate of response under treatment with biological agents should be validated in prospective trials.

Key words: ovarian cancer, follow-up, CA125

Introduction

Epithelial ovarian cancer (EOC) is the fourth cause of cancer-related death in women [1]. Despite optimal upfront treatment, 75% of all EOC patients will develop recurrence of the disease, often within the first 2 years after diagnosis, but with differing proportions depending on the initial stage at diagnosis (20%–30% in early-stage disease and 50%–95% in advanced-stage disease). Patients treated for EOC usually undergo a follow-up in order to detect recurrence of the disease, although there is no evidence that the current follow-up procedure increases survival.

Follow-up assessment in patients treated for EOC generally consists of physical and gynecological examination, serum cancer antigen 125 (CA125), ultrasound, and other imaging examinations.

Use of CA125 in ovarian cancer management

The CA125 antigen is a high-molecular-weight glycoprotein, which is expressed by a large proportion of EOC. It is detected by the OC125 monoclonal antibody, which is obtained after immunization with the OVCA 433 cell line (derived from the ascites of a patient with papillary cystadenocarcinoma of the ovary) and was first described by Bast et al. in 1981 [2]. This large glycosylated mucin molecule is present within normal ovarian tissue and on the epithelium of the endometrium, endocervix and fallopian tubes; however, its precise cellular function is as yet unknown [2].

Since its discovery, CA125 has become well established as a tumor marker for EOC, and has shown to have an important role in initial diagnosis, during therapy as a surrogate of clinical response and during follow-up.

The sensitivity and specificity of CA125 at initial diagnosis is known to be poor. It is only raised in 50% of stage I EOCs and in 75%–90% of patients with advanced disease [2]. False positive results have been noted in many medical disorders, both malignant and benign.

CA125 has been proposed and widely adopted as a tool for the assessment of response during therapy [3]. The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines are also commonly used in ovarian cancer to evaluate the effectiveness of the therapy given [4]. Unfortunately, diagnostic imaging is not always able to accurately measure the multiple small peritoneal lesions typical of this disease or the so-called ‘nonmeasurable lesions’; hence the choice of CA125 as a surrogate for monitoring the treatment of ovarian cancer [5].

The currently accepted criteria defined by Rustin et al. and the Gynecologic Cancer InterGroup (GCIG) [6] defines three categories of response: ‘complete response’ as normalization of CA125 on two serial tests ≥1 month apart with no evidence of
disease on imaging; ‘partial response’ as 50% decrease over two serial CA125 measurements ≥28 days apart; and ‘progressive disease’ as doubling of CA125 concentration from the patient’s nadir. This procedure requires two pretreatment samples, the last within 1 week of starting therapy. The evaluation of response during treatment requires CA125 levels ≤50% of the basal value; this value has to be confirmed with another assay after 21 days. The situation is considered not evaluable if there is interference with the pleura/peritoneum in the previous 28 days or when the patient received mouse antibodies [6].

Gronlund et al. [7] validated the GCIG CA125 response criteria by comparing the prognostic value of response according to the CA125 definition with that obtained using RECIST guidelines. In 131 patients who received topotecan or paclitaxel plus carboplatin as second-line chemotherapy for ovarian cancer, they found that the CA125 criteria were 2.6 times more accurate than RECIST at predicting survival. Although univariate analysis both RECIST and CA125 response were each significantly correlated with survival, in a Cox analysis, where both response classifications were included in the regression model, only the CA125 response remained significant [7].

The absolute level of CA125 before therapy has also been shown to be of prognostic importance [8, 9]. Moreover, the serum half-life of CA125 during initial chemotherapy has been shown to be an independent prognostic marker for survival, rate of progression, time to progression and the chance to achieve complete remission [10, 11].

Zorn et al. [12], taking data from seven prospective randomized clinical trials conducted by the Gynecologic Oncology Group (GOG), found that the pretreatment CA125 level was an independent predictor of progression-free survival (PFS) in patients with advanced EOC who received a standard chemotherapy regimen, particularly in the setting of disease that was debulked to a microscopic residual and in the serous or endometrioid subtypes. The nadir CA125 value at the end of first-line chemotherapy, as proposed by Crawford and Peace [13], appears to be an important way to stratify patients according to their risk of progression in clinical trials. In this paper the nadir value of CA125 was categorized into three arbitrary groups: group A, ≤10 U/ml; group B, 11–20 U/ml; and group C, 21–30 U/ml. Seventy-nine patients who attained levels <30 U/ml were scrutinized [13]. The results of this study, although coming from a small sample of patients and although the cut-off was set arbitrarily, show that for patients with CA125 values ≤10 U/ml (group A) there is an excellent prognosis after chemotherapy. Indeed, the time to biochemical progression (defined as the interval between the nadir and progression) and overall survival (OS) were significantly longer in group A compared to group B and C [13].

A prognostic role of nadir CA125 was also described by van Altena et al. [14], who showed that in 331 patients with no physical or radiological signs of residual disease and normal CA125 values (<35 U/ml) after standard primary treatment, those with a CA125 nadir value of ≤5 U/ml had a significantly longer PFS and OS.

For decades, CA125 has been used worldwide as a tool for the early detection of recurrence. More than half of the women treated for advanced ovarian cancer with surgery and chemotherapy will experience a complete clinical response with normalization of CA125 levels and without evidence of macroscopic disease at imaging studies.

Rising serum CA125 levels precede the clinical detection of relapse in 56%–94% of cases, with a median lead time of 3–5 months [15]. However, CA125 is not optimally sensitive and up to 50% of patients with normal levels of CA125 after chemotherapy were found to have small volumes of persistent disease at second-look surgery. An elevated and rising CA125 level of 2×ULN is indicative of progression in the vast majority of patients, and there is a well-accepted GCIG definition of CA125 progression [16, 17]. The GCIG criteria for CA125 progression are as follows: (i) patients with elevated CA125 prior to treatment and normalization of CA125 during treatment must show an increase of CA125 ≥2×ULN on two occasions ≥1 week apart; (ii) patients with elevated CA125 prior to treatment, which does not normalize with treatment, must show a CA125 increase of at least twice the nadir value on two occasions ≥1 week apart; or (iii) patients with CA125 in the normal range prior to treatment must show a CA125 increase of ≥2×ULN on two occasions ≥1 week apart [16].

Data in the literature indicate that the specificity and the sensitivity of radiological assessment by PET, MRI and CT nowadays reduce the proportion of asymptomatic patients with an isolated increase in CA125 levels, with a possible anticipation of the diagnosis of recurrence of about 2 months before the onset of symptoms [18, 19] (Figure 1).

The common belief that earlier detection and treatment of ovarian cancer can result in better outcome for patients has been the goal of important research in the last decade. The regular measurement of CA125 during follow-up is one of the best examples in oncology of a test that can detect the recurrence of cancer months before symptoms or signs of recurrence occur. The sensitivity of CA125 in the detection of recurrence is ~90% [15]. However, although most women can expect a good response and improved survival with chemotherapy for their first recurrence, it is rarely curative and causes side-effects. Thus, concerns about CA125 testing and the implications of an elevated CA125 are major sources of anxiety.

The MRC OV05/EORTC 55955 trial was designed to investigate the benefit of early chemotherapy for relapsed disease on the basis of CA125 levels alone, as opposed to

![Figure 1. Time line of follow-up and start of treatment in patients with CA125 alone, asymptomatic.](image-url)
treatment triggered by symptoms [20]. The primary outcome of the study was OS, and secondary outcomes included time to second-line chemotherapy, time to third-line treatment or death, and quality of life. Just over 500 patients were randomized to either immediate treatment on the basis of rising CA125 levels or delayed treatment at the onset of symptoms. After completion of first-line chemotherapy, CA125 levels were measured every 3 months, but patients and the treatment team were blinded to the results, which were monitored centrally by the trial center. When the levels were >2x ULN, the patients were randomized to immediate treatment or to continue with the blinded CA125 measurements with treatment delayed until the patient developed symptoms. The median time from registration to randomization was 9 months. Patients in the early-treatment group started second-line chemotherapy 4.8 months earlier than the delayed-treatment group and third-line chemotherapy started 4.6 months earlier in the early-treatment group. Despite this anticipated treatment, there was no difference in survival outcomes in the two groups, which was contrary to what many people expected. Moreover, earlier treatment based on CA125 levels alone was also associated with an earlier deterioration in patients’ quality of life. The trial results challenge the widespread belief that earlier treatment of recurrent EOC must be better and in some way also question the role of follow-up in general in this disease.

Based on these results the authors [20] have suggested that CA125 should not be prescribed to all patients with ovarian cancer during follow-up. The trial has important merits, since it is the first time that women can be given evidence-based advice and make informed choices regarding follow-up. Rustin et al. [20] suggest that women can be informed that there is no evidence of a benefit from early treatment based on rising CA125 levels and no deterioration in quality of life by delaying chemotherapy. They indicated that women should be told that if their CA125 rises during follow-up, chemotherapy can be safely delayed until required due to symptoms or signs of tumor recurrence. Also, according to these authors, regular CA125 monitoring is likely to remain a requirement in certain clinical trials but women who have regular CA125 measurements might now wish not to be told their results. On the other hand, despite these trial results some women may choose to continue with regular CA125 monitoring as an aid to planning their life. Whatever the patient’s own choice, the results of this trial suggest that they could be advised against routine CA125 monitoring if their disease is in complete remission following first-line treatment, but be reassured that if they develop any signs suspicious of tumor relapse or are worried about relapse they will have rapid access to CA125 measurement.

Our point of view is that although there is no doubt that regular measurements of CA125 will diagnose recurrence well before symptoms occur in most patients and although early therapy with the drugs available nowadays will not improve OS, it is possible that earlier treatment in selected patients may delay the onset of cancer-related symptoms, such as those associated with the development of ascites or bowel obstruction, which both have a negative impact on quality of life. Delay of symptomatic progression is in our view an important endpoint in this patient population. Moreover, the patient who is ‘waiting for symptoms’ to occur may well have significant anxiety and may recur to the physician for any unspecific symptom.

CA125 measurement during follow-up can help to screen the patients who should undergo imaging. In fact, we still believe that independently from the results of the Medical Research Council (UK) (MRC)/European Organisation for Research and Treatment of Cancer (EORTC) trial, patients with radiological evidence of disease progression should start treatment without waiting for symptom onset. Although this is a palliative treatment, the response rate to chemotherapy is correlated with the disease burden, and patients with symptoms have a large burden and often invalidating conditions that prevent them obtaining optimal palliative benefit from the therapy [21]. On the hand, patients with an increase of CA125 alone without radiological evidence of disease are candidates for clinical trials and there is agreement that they should not be treated in routine practice.

One of the major criticisms against the MRC/EORTC trial is that very few patients with recurrent disease had received surgery. Although no prospective randomized trial has demonstrated a survival effect of surgery in recurrent disease, patients who undergo complete secondary cytoreduction, i.e. leaving no macroscopic residual disease behind, have a clear advantage in terms of PFS and OS, as underlined in several retrospective studies [22, 23].

A meta-analysis suggested that optimal resection of recurrence at secondary cytoreductive surgery could prolong survival in selected cohorts of patients [24]. Several factors influence the ability to completely resect recurrent disease, including the number and size of disease sites, the presence of ascites and/or carcinomatosis, and the disease-free interval. In the study by Fleming et al. [22], a shorter time interval between CA125 elevation and secondary cytoreductive surgery correlated with a greater incidence of optimal resection, resulting in a longer median disease-free interval and OS (47 versus 23 months, $P \leq 0.0001$). For patients who ultimately underwent suboptimal surgery, Fleming et al. observed a median time interval of 16.4 weeks from the time their CA125 started to increase; each week delay after the first CA125 elevation correlated with a 3% increased chance that the resection would be suboptimal [22].

One can argue that there are no published randomized controlled trials to date demonstrating a survival advantage with secondary cytoreductive surgery. A trial is ongoing on this topic: the AGO DESKTOP 3. The study is based on the evidence of the retrospective assessment and validation of the DESKTOP score, based on the presence of ascites, optimal cytoreduction at primary surgery and performance status [25].

Thus, CA125 follow-up can be used to screen patients who should undergo imaging assessment. This may help to select the patients who may benefit from surgery and early therapy. We believe that in a system where economical resources are limited, the availability of a sensitive tool for selecting patients who should receive expensive radiological examinations is a worthwhile method that should not be abandoned.
implications for clinical research in ovarian cancer

In the last decades there has been increasing interest in the use of biological agents in the management of ovarian cancer. However, the evaluation of tumor response during treatment with biological agents is difficult, both with RECIST and CA125 criteria. In fact, the morphological changes of the tumor do not always correspond to changes in tumor size. As for CA125, the biochemical modulation of the tumor may alter the production and/or secretion of the mucin MUC16, which is recognized by the OC125 antibody. In fact, the mechanism of regulation of MUC16 expression has not yet been explained.

Recently, Azad et al. [26] reported the results of a trial with sorafenib and bevacizumab in 42 patients with EOC evaluated both by RECIST and CA125 response criteria. Although the number of patients in this study was small, the results showed that changes in CA125 were not in close agreement with the objective response at imaging (only 67% concordance). These authors concluded that molecular-targeted therapies may affect CA125 concentrations differently from traditional chemotherapy with cytotoxic agents, probably because these agents may modulate CA125 production and secretion, and, thus, possibly affect its reliability [26, 27]. We strongly believe that both criteria should be prospectively evaluated in clinical trials and that this is an important goal for future research.

The Vancouver GCIG Consensus Conference (2010) also stated that patients with asymptomatic CA125 recurrence may be candidates for studies with new agents [28]. Although early treatment with available therapies does not prolong survival, new therapies may be more efficacious. An increase in CA125 is a sign of active disease and we should learn how to treat these patients, aiming at an improved survival. An example of a study in this category of patients is GOG study no. 198, which compared tamoxifen and thalidomide in women with recurrent International Federation of Gynecology and Obstetrics (FIGO) stage III or IV EOC who had completed first-line chemotherapy and who subsequently had GCIG-documented CA125 progression. Women who received thalidomide had a 31% increased risk of disease progression (hazard ratio, 1.31) compared with those who were given tamoxifen. The median PFS was 3.2 months in the thalidomide group versus 4.5 months in the tamoxifen group. Although this was a relatively small study, it does suggest a difference between the two arms of the study and exemplifies the sort of studies that may be carried out in this population. Another example is the recently presented study of pazopanib, an oral multitarget antiangiogenic agent, in patients with ‘CA125 recurrence’. In this study, Friedlander et al. [29] showed an interesting CA125 response rate, which ultimately was the basis for a study of pazopanib as maintenance after first-line chemotherapy (AGO-OV16 trial). Thus, this population of asymptomatic patients with CA125 increase may be an ideal setting to investigate the activity of new drugs.

conclusions

CA125 has been used for decades in ovarian cancer during follow-up, where it is able to identify a percentage of patients with asymptomatic recurrence. Although a recent MRC/EORTC trial has demonstrated that early treatment with chemotherapy in asymptomatic patients based on CA125 increase does not prolong survival, we still believe that CA125 monitoring should be prescribed to patients during follow-up. In fact, it can help to identify patients who should undergo radiological examination in order to select those who may benefit from surgery or from early treatment before the onset of symptoms. We believe that the delay of important symptoms, such as those associated with ascites or bowel occlusion, is an important goal of the treatment of recurrent ovarian cancer. In patients with asymptomatic CA125 increase, more effective therapies able to improve survival are needed and these patients may be eligible for clinical trials, as stated by the 2010 Vancouver GCIG Consensus Conference.

acknowledgements

Dr Pignata is recipient of a grant from Associazione Italiana per la Ricerca sul Cancro. The authors thank Dr A. Trocino, Librarian of the National Cancer Institute of Naples ‘G. Pascale’, for the bibliography assistance.

disclosures

The authors have declared no conflicts of interest.

references


