Serum markers as prognostic factors in epithelial ovarian cancer: an overview

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Summary

A comprehensive review of the literature and the authors' personal experience on serum determination of tumour markers in epithelial ovarian cancer can be summarised as follows:

– CA 125 is the most reliable marker for monitoring the course of epithelial ovarian cancer;

– CA 125 assay is not an adequate screening test for this malignancy but it can represent an useful adjunct to clinical examination and ultrasound in the differential diagnosis of ovarian masses in postmenopausal women;

– Serial measurements of CA 125 are useful in monitoring the response to chemotherapy and follow-up. In patients with preoperative positive CA 125 assay, the concomitant determination of other tumour markers does not add further information when compared to CA 125 alone. Conversely in patients with preoperative negative assay the measurement of one or more of other antigens could be of clinical relevance.

Introduction

In the 1980's a wide application of monoclonal antibody technology led to the identification of several ovarian cancer-associated antigens, whose serum measurement could offer useful biochemical tools for diagnostic evaluation and management of this tumor. CA 125 is the most reliable marker for ovarian cancer. However, other serum antigens, such as CA 19-9, CA 15-3, and TAG-72, have been assessed in patients with this malignancy.

Clinical - Experimental results

CA 125

CA 125 is an antigenic determinant recognized by a murine mono-clonal antibody against a human ovarian carcinoma cell line [1]. Elevated serum CA 125 levels at diagnosis can be found in 50% of patients with FIGO stage I and in 90% of those with FIGO stage II-IV ovarian cancer [2]. Therefore serum CA 125 assay alone is not an adequate screening test because the goal of screening is to detect early disease [3]. Moreover, a significant proportion of women with benign conditions, such as endometriosis [4] or pelvic inflammatory disease [5], have raised antigen levels resulting in relatively low specificity for this test.

Mucinous ovarian cancer often fails to express CA 125, as evidenced by immunohistochemical [6, 7] and serological studies [8, 9]. For instance, in our experience [10] preoperative CA 125 levels were >35 U/ml in 84.6% of 78 patients with nonmucinous and in 66.7% of 12 patients with mucinous tumors. The corresponding sensitivity values using 65 U/ml as a cut-off were 79.5% and 50.0% (p=0.0037), respectively.

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Serum CA 125 assay has been assessed as a useful biochemical tool for both differential diagnosis of adnexal masses and monitoring and prognostic evaluation of patients with ovarian cancer.

CA 125 in the differential diagnosis of ovarian masses

Preoperative serum CA 125 assay has been correlated with the risk of malignancy of an ovarian mass [2, 8-14]. First, Einhorn *et al.* [8] found serum CA 125 >35 U/ml and >65 U/ml in 100% and 81%, respectively, of patients with nonmucinous ovarian cancer compared to 6% and 1%, respectively, of patients with benign ovarian diseases. Subsequent papers reported that serum CA 125 assay had a sensitivity of 78%-100% and a specificity of 60%-78% using the value of 35 U/ml as a cut-off, and respectively, a sensitivity of 56%-93% and a specificity of 80%-92% using 65 U/ml as a cut-off [10-14].

Malkasian *et al.* [12] detected that sensitivity and specificity were higher in postmenopausal than in premenopausal women. We noted that sensitivity was higher for patients over 50 years of age than in younger ones (with 65 U/ml as a cut-off = 81.1% vs 50%, p=0.01), whereas specificity was similar in the two groups [10].

Finkler *et al.* [15] observed that serum CA 125 increased the diagnostic reliability of clinical examination and abdominal ultrasound in the preoperative assessment of ovarian masses in postmenopause. Similarly we found that serum CA 125 plus abdominal ultrasound had a higher sensitivity and a similar specificity when compared to ultrasound alone in women older than 45 years of age [16].

Two large multicentric European studies assessed the clinical value of the CA 125 test in the differential diagnosis of pelvic masses in postmenopausal women [17, 18]. An Italian study on 290 patients revealed that the diagnostic accuracy of serum CA 125 (cut-off = 65 U/ml) was 83%, of abdominal ultrasound 81%, and of serum

CA 125 plus ultrasound 94% [17]. Therefore the association of abdominal ultrasound and serum CA 125 might support the clinical judgment. A Dutch study on 228 patients showed that the accuracy of clinical examination, transvaginal ultrasound, and serum CA 125 assay (cut-off = 35 U/ml) was quite the same (76%, 74%, and 77%, respectively) [18]. However it is noteworthy that no cancer was found in patients in whom all three tests were negative. In a study performed on 109 patients scheduled for laparotomy for an adnexal mass, our group found that in premenopause the diagnostic accuracy of transvaginal ultrasound (97%) was higher than that of color flow imaging (73%, $p<0.002$) and serum CA 125 (cut-of = 65 U/ml) (87%, $p<0.05$), whereas in postmenopause the three tests showed a similar accuracy (85%, 82%, and 79%, respectively) [19]. Therefore the addition of further tests besides transvaginal ultrasound is not warranted in premenopause, whereas they seem to be useful in postmenopause.

Most ovarian masses in postmenopause will require surgical evaluation [3]. A possible exception may be represented by women with a subclinical cyst detected on ultrasound, which is unilocular, less than 5 cm in diameter, and associated with normal serum CA 125. Conversely, patients with a suspect mass should be promptly referred to a specialized oncologic center for optimal surgical management.

CA 125 in the monitoring of disease course

Among ovarian cancer patients, changes in CA 125 levels have been found to correlate with regression, stability, and progression of disease in 87%-94% of instances [20-23]. Elevated CA 125 values at the time of second-look are strong predictors of residual disease, while normal antigen levels can be associated with both positive and negative second-look findings [23-26].

Lavin *et al.* [27] reported that 64% of 14 patients with serum CA 125 <35 U/ml after three months from the start of chemotherapy achieved a pathological complete response, while persistent disease after the end of treatment occurred in all 13 patients with serum three-month CA 125 >35 U/ml. Mogensen *et al.* [28] observed that the incidence of increased (>35 U/ml) CA 125 levels after the second and third cycle of chemotherapy was significantly higher in patients who had residual disease at second-look than in those who achieved a pathologically complete response. In the series by Hawkins *et al.* [29] serum CA 125 half-life was the most important prognostic factor for the chance of achieving a complete response ($p=0.01$).

In an Italian multicentric CTF study on 225 patients with advanced ovarian cancer, both serum CA 125 value before the third cycle of platinum-based chemotherapy and serum CA 125 half-life during chemotherapy were independent prognostic variables for the chance of obtaining a pathologically complete response [30].

Patients with a CA 125 half-life <25 days had a 3.6 times as great a probability of achieving a pathologically complete response than the ones with a longer half-life. Therefore the calculation of CA 125 half-life during early chemotherapy could detect a poor prognosis subset of patients for whom a more aggressive therapy might be of benefit.

Serum CA 125 assay is very useful for the early detection of recurrent disease, since a progressive elevation of antigen levels may precede the clinical diagnosis of relapse in 56%-94% of cases with a lead time of 3-5 months [23, 25, 31-35]. However a negative CA 125 test does not exclude the presence of recurrent tumor. For instance Forstner *et al.* [36] reported that serum CA 125 was raised only in 54% of recurred patients, and in particular, in 69% of those with residual disease >2 cm.

The optimal management of ovarian cancer patients with rising CA 125 levels and no clinical, ultrasonographic, and radiological evidence of disease has not yet been defined [37]. Response to chemotherapy can be better in patients with small lesions and good performance status. However, the early administration of chemotherapy at the time of CA 125 elevation is associated with a greater anxiety due to an earlier knowledge of disease status. Moreover, drug-related toxicities can be heavier the lower the time interval is from the first chemotherapy. A prospective randomized multicentric trial comparing early chemotherapy versus observation is warranted in order to assess whether earlier detection of recurrent disease given by CA 125 monitoring can improve patient outcome.

Prognostic relevance of CA 125 levels - 1) Preoperative CA 125

The prognostic value of preoperative CA 125 levels is still uncertain. Most series [30, 38-40] have reported that preoperative CA 125 value had no clinical relevance, whereas Mobus *et al.* [41] detected that survival was significantly greater for patients with preoperative serum CA 125≤65 U/ml compared to those with higher levels.

2) Postoperative decline in CA 125 levels

Some authors [42-44] have reported that postoperative drop in CA 125 levels correlated with the size of residual disease. In particular, Brand and Lidor [44] found that postoperative antigen concentrations, measured 3-14 days after surgery, declined more than 60% from preoperative levels in all the 22 patients with residual disease <2 cm and less than 60% in all the 5 patients with residuum >2 cm ($p<0.001$). On the other hand, Yedema *et al.* [45] observed that CA 125 levels in the early postoperative period did not always reflect the outcome of cytoreduction. In fact in their series debulking surgery caused a postoperative decline in antigen concentrations only in patients with relatively high preoperative serum CA 125. Conversely, rising postoperative antigen levels were often detected in patients with relatively low preoperative serum CA 125. In an Italian CTF study on 46 patients with advanced ovarian cancer the postoperative drop in serum CA 125 was significantly higher in patients who were optimally cytoreduced than in those who were left with bulky residual disease [46]. CA 125 decline correla-

ted with tumor residuum at any preoperative serum CA 125 value. However, even in the subset of patients with preoperative serum CA 125 >400 U/ml, the percentage of reduction in antigen levels did not allow discrimination with an accuracy of 100% between patients with residual disease below or above 2 cm. Surgery is able to exert contrasting effects on CA 125 levels. In fact tumor debulking and drainage of ascites cause a fall in CA 125 levels, whereas peritoneal damage and surgical manipulation determine an increase in antigen concentrations [45, 47-49]. The former phenomena can become predominant in patients with elevated preoperative CA 125 levels. Therefore in such patients the decline in serum CA 125 correlates with residual disease better than in patients with normal or moderately raised antigen concentrations.

3) Decline in CA 125 levels during chemotherapy

The decline of CA 125 levels during early chemotherapy has been found to correlate with patient survival.

Sevelda *et al.* [39] measured serum CA 125 three months after surgery in 132 patients with FIGO stage I-IV ovarian cancer, and detected that it was the strongest independent prognostic factor for survival (p=0.0006). Fayers *et al.* [50] assessed the data from 248 patients with FIGO stage I-IV disease, and found that the absolute value of serum CA 125 before the third cycle of chemotherapy was the single most important factor for predicting progression at 12 months.

Van der Burg *et al.* [51] calculated serum CA 125 half-life in 37 patients with FIGO stage I-IV ovarian cancer, and detected that patients with a half-life ≥20 days had a 3.2 times as high a progression rate (p=0.01) and a significantly shorter median time to progression (11 months vs 43 months) when compared to patients with a shorter half-life. Other authors confirmed that serum CA 125 half-life was significantly related to survival [29, 30, 52, 53]. In particular, in the CTF series antigen half-life was the strongest independent prognostic variable for survival (p=0.007) after residual disease (p=0.0001) [30].

4) CA 125 levels at the time of recurrence

The clinical outcome of patients with recurrent ovarian cancer is very poor since salvage therapy is largely unsuccessful. Makar *et al.* [54] reported that serum CA 125 value at relapse was related to further survival in 135 patients with recurrent disease who had different salvage treatments. Patients with normal serum CA 125 (<35 U/ml) at the time of recurrence had a better survival than those with elevated levels (p<0.01). Conversely in the Italian CTF study assessing 60 recurred patients who received salvage chemotherapy with or without surgery, survival after relapse was significantly related to time to recurrence but not to CA 125 level at relapse or any other examined variable [55].

Other tumor-associated antigens

Several tumor-associated antigens, first identified in gastrointestinal or breast cancer, such as CA 19-9, CA 15-3, and TAG-72, have been subsequently detected in tissue sections and serum from ovarian cancer patients.

Given the evolutive potential of the mullerian epithelium from which different histological types of ovarian cancer can arise, the simultaneous determination of several tumor markers may be helpful in the management of patients with this malignancy [56, 57].

CA 19-9 is a carbohydrate determinant recognized by a monoclonal antibody against a human colon carcinoma cell line and subsequently detected in tissue sections from ovarian carcinomas, particularly of mucinous histotype [58, 59].

CA 15-3 is a breast cancer-associated antigen identified by two monoclonal antibodies, termed 115D8 (reacting with the glyocoprotein MAM-6 expressed by most carcinomas) and DF3 (reacting with an antigen present in a membrane-enriched fraction of metastatic breast cancer) [60, 61].

TAG-72 is a mucin-like glycoprotein recognized by a monoclonal antibody against a membrane-enriched fraction of human breast carcinoma cells, and subsequently detected in serous, mucinous, and undifferentiated ovarian carcinomas [62, 63].

Other antigens in the differential diagnosis of ovarian masses

Elevated CA 19-9 levels have been found in 17%-35.6% of ovarian cancer patients [10, 20, 64]. Canney *et al.* [64] noted CA 19-9 levels >33 U/ml in 25.5% of patients with nonmucinous and in 50.0% of those with mucinous tumors. In our experience, serum CA 19-9 was >40 U/ml in 35.6% of 90 patients with ovarian cancer, and in particular in 83.3% of patients with mucinous and in 28.2% of those with nonmucinous carcinomas [10]. False positive CA 19-9 values were found in 18.9% of 254 patients with benign ovarian diseases, and in particular in 22.1% of 68 patients with endometriotic cysts, and in 45.5% of 33 patients with benign cystic teratoma. It is noteworthy that the association of serum CA 125 (cut-off = 65 U/ml) and CA 19-9 had a higher sensitivity (93.2% vs 81.1%, p=0.03) and a slightly lower specificity (78.9% vs 86.0%, p=ns) when compared to CA 125 assay alone in the differential diagnosis of ovarian masses in patients older than 50 years. Scambia *et al.* [65] found CA 15-3 levels >30 U/ml in 70.7% of 58 patients with ovarian cancer, and in detail in 75.0% of nonmucinous compared to 50.0% of mucinous malignancies. We detected CA 15-3 values >32 U/ml in 57.1% of patients with ovarian cancer, and in detail in 64.6% of patients with nonmucinous and in 16.7% of those with mucinous carcinomas [10]. Therefore CA 15-3 was less sensitive than CA 125 for nonmucinous and even less for mucinous malignancies. False positive CA 15-3 values were found in 6.1% of patients with benign ovarian diseases.

In the paper by Soper *et al.* [14] serum TAG-72 was > 10 U/ml in 58% of 33 patients with ovarian cancer compared to 4% of 46 patients with benign pelvic diseases. We detected TAG-72 values > 3.8 U/ml in 70.7% of 75 patients with ovarian cancer, and in particular in 70.3% of patients

with nonmucinous and in 72.7% of those with mucinous carcinomas [10]. Thus TAG-72 was less sensitive than CA 125 for nonmucinous and more sensitive for mucinous malignancies. False positive TAG-72 values were noted in 8.2% of patients with benign ovarian diseases.

In our early experience, the combined evaluation of abdominal ultrasound plus serum CA 125 and serum CA 19-9 or TAG-72 had a higher sensitivity (94% vs 81%, p=0.04) and a not significantly different specificity when compared to ultrasound alone in the differential diagnosis of ovarian masses in postmenopause [66]. However, according to a recent multicentric Italian study [67] the association of serum CA 125 and TAG-72 failed to significantly improve the results obtained with serum CA 125 assay alone in the preoperative evaluation of pelvic masses in postmenopausal patients.

Other antigens in the monitoring of disease course

There are few data in the literature on the ability of tumor-associated antigens other than CA 125 to reflect the disease course in ovarian cancer.

Bast *et al.* [20] reported that changes in CA 19-9 levels correlated with tumor progression or regression in 33% of instances, and that the combined evaluation of serum CA 125, CA 19-9 and CEA was not superior to serum CA 125 assay alone in the monitoring of disease. On the other hand, Canney *et al.* [64] noted that the measurement of serum CA 19-9 gave additional information to that of serum CA 125 in the management of patients. Yabushita *et al.* [56] reported that the simultaneous determination of CA 125 with other markers, such as TPA, IAP, CEA, and ferritin, was more useful than CA 125 assay alone for monitoring ovarian cancer [56]. In the series by Scambia *et al.* [65] CA 15-3 values reflected the clinical course of disease in 87% of patients.

We found that changes in serum levels of CA 125, CA 19-9, CA 15-3, and TAG-72 correlated with the disease course in 87.4%, 76.3%, 71.3%, and 76.0% of instances, respectively, in ovarian cancer patients [23]. Similarly to CA 125, normal other antigen levels after the sixth cycle of chemotherapy were associated with both complete response and persistent disease at second-look, while elevated values were quite invariably indicative of residual tumor. Among patients with elevated antigen levels at diagnosis, the clinical detection of neoplastic progression after primary treatment was proceded by a rise in serum CA 125 in 93.3% of cases (median lead time, 5 months; range, 1-14 months), of serum CA 19-9 in 80.0% of cases (median lead time, 3 months; range, 2-4 months), of serum CA 15-3 in 66.7% of cases (median lead time, 2 months; range, 1-6 months), and of serum TAG-72 in 81.8% of cases (median lead time, 5 months; range, 1-12 months). By assessing in detail the patients with preoperative elevated levels of both CA 125 and some of the other antigens, we confirmed that serum CA 125 reflected the clinical course of disease better than the other markers, and that CA 125 usually increased earlier or in a higher percentage of cases than the other antigens before the clinical detection of recurrence.

Conclusions

CA 125 is the most reliable marker for ovarian cancer in clinical practice. Serum CA 125 assay is not an adequate screening test for this malignancy, but it can represent an useful adjunct to clinical examination and ultrasound in the differential diagnosis of ovarian masses particularly in postmenopausal women. Because of the different antigen expressions by nonmucinous and mucinous malignancies, the association of serum CA 125 and CA 19-9 has a significantly higher sensitivity in the preoperative evaluation of ovarian enlargements in postmenopause.

Serial measurements of CA 125 are very useful in monitoring the response to chemotherapy and follow-up of patients with ovarian cancer. In patients with preoperative positive CA 125 assay, the concomitant determination of other tumor markers does not add further information when compared to CA 125 alone. Conversely in patients with preoperative negative CA 125 assay, the measurement of one or more of the other antigens could be of clinical relevance. In particular the determination of serum CA 19-9 or TAG-72 could be useful in the monitoring of patients with mucinous ovarian cancer, which often fails to express CA 125.

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