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Has serum CA 125 assay at the time of relapse a prognostic relevance for patients with recurrent ovarian carcinoma after primary cytoreduction and platinum- and paclitaxel-based chemotherapy?

A. Gadducci, M. Notarnicola, A. Menichetti, N. Lanfredini, A. Fanucchi, S. Cosio

Department of Experimental and Clinical Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa (Italy)

Summary

Purpose of investigation: To correlate serum CA125 at relapse with survival in ovarian cancer patients who achieved a complete response after primary cytoreduction and paclitaxel- and platinum-based chemotherapy. *Materials and Methods:* The study was conducted in 104 patients. *Results:* The 25%, 50%, and 75% quantiles of CA125 levels at relapse were 46, 118, and 190 U/ml. By log-rank test, survival after recurrence was related to consolidation treatment ($p = 0.046$), platinum-free interval (PFI) ($p < 0.000005$), number of recurrence sites ($p = 0.03$), treatment at recurrence ($p = 0.002$), and serum CA125 taking 118 U/ml as cut-off ($p = 0.013$). On multivariate analysis, consolidation treatment ($p = 0.007$), PFI ($p = 0.0001$), treatment at recurrence ($p = 0.01$), and serum CA125 taking 118 U/ml as cut-off ($p = 0.04$) were independent prognostic variables for survival. *Conclusions:* Serum CA125 at relapse was an independent prognostic variable. Patients with serum CA125 >118 U/m had 1.943 higher risk of death than those with lower antigen value.

Key words: Ovarian carcinoma; CA125; Chemotherapy; Secondary cytoreductive surgery; Survival after recurrence.

Introduction

Primary cytoreductive surgery plus platinum- and paclitaxel-based chemotherapy are the keystones of treatment of advanced ovarian carcinoma, able to achieve a clinical complete response rate and a pathological complete response rate of 50% and 25–30%, respectively [1-5]. Approximately 75% of clinically complete responders and 50% of pathologically complete responders will relapse after a median time of 18–24 months [6]. Patients with recurrent disease usually experience a poor prognosis, with a median survival after recurrence of less than two years [2, 6]. The clinical outcome of patients with recurrent disease is strictly dependent on platinum-free interval [PFI], defined as the interval from the last date of platinum dose until documented progressive disease [7-14]. Other variables have been assessed as predictors of response to further treatment and of post-recurrence survival, such as tumour histology [15,16], tumour burden [15-17], and haemoglobin level [10, 15-17]. Very few and conflicting data are available in the literature about the prognostic significance of serum CA 125 assay at recurrence [18-22]. In the present investigation, serum CA 125 levels at the time of relapse were related to survival after recurrence in patients with advanced ovarian carcinoma who achieved a complete response after primary cytoreduction and paclitaxel- and platinum-based chemotherapy and who subsequently developed recurrent disease.

Materials and Methods

The authors reviewed the hospital records, including surgical notes and pathological reports, of 104 consecutive patients with recurrent ovarian carcinoma treated at the authors' Department between March 1996 and November 2013. The study included only patients who: 1) had advanced disease at presentation, 2) achieved a complete clinical or pathological response after primary cytoreduction and six cycles of paclitaxel- and platinum-based chemotherapy, and 3) who subsequently developed a recurrence. Patients who underwent neoadjuvant chemotherapy followed by interval debulking surgery, as well as those who achieved a complete clinical response but who were found to have microscopic or macroscopic residuum at second-look, were excluded from the analysis. An asymptomatic patient with rising CA 125 levels and negative clinical and imaging examinations was not still considered to have recurrent disease and underwent a more stringent follow-up programme.

The tumour stage and histological diagnosis of each case were determined according to FIGO criteria and the histological typing system of the World Health Organization (WHO), respectively [23]. Tumours were graded as well (G_1), moderately (G_2), or poorly (G_3) differentiated.

After the sixth cycle of chemotherapy, patients with no evidence of disease at clinical, sonographic, and radiological examination and with serum CA 125 < 35 U/ml were defined to be in complete

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clinical response. Three to five weeks after the end of chemotherapy, a second-look laparotomy or laparoscopy was often proposed to clinically complete responders until 2006, mostly to patients enrolled in clinical trials. A pathological complete response at second-look was defined as the disappearance of all macroscopic tumor deposits with negative peritoneal washing and negative multiple random biopsies. Several clinically or pathologically complete responders received consolidation treatment.

All patients were periodically followed-up until they died or until May 2014. Clinical examination, abdomen- pelvic ultrasound and CA 125 assay were performed every three to four months during the first two years, every six months from the third to the fifth year, and yearly afterwards. Abdomen pelvic-computed tomography and chest X-rays were carried out yearly until the fifth year. Further investigations where performed when indicated.

The serum levels of CA125 were determined with immunoradiometric assays or with enzyme immunoassays using commercially available kits. The manufacturer's reagents were used with standard quality control procedures to ensure comparability. The upper limit of normal was 35 U/ml for all assays used. The median follow-up of survivors was 43 (range 7−183) months.

Patient characteristics at initial diagnosis (date, FIGO stage, histological type, tumour grade, residual disease after initial surgery, first-line chemotherapy, second-look surgery, consolidation treatment) and at the time of relapse (date, age of patient, site of recurrence, number of recurrence sites, serum CA 125 at recurrence, treatment at recurrence) were reported for each case.

Statistical analysis

SPSS ver.13 Inc Chicago IL was used for computations. The time from detection of the first recurrence to death or last observation was defined as survival after recurrence. The analysed prognostic variables included FIGO stage, histological type, tumour grade, residual disease after initial surgery, second-look surgery, consolidation treatment, PFI, sites of recurrence, number of recurrence sites, serum CA 125 at recurrence, and treatment at recurrence.

Survival analysis was performed according to the Kaplan-Meier product-limit method. Differences between groups were evaluated by the log-rank test. A multiple regression analysis based on the Cox proportional hazard model was used to jointly test the relative importance of variables as predictors of survival times.

Table 1. — *Patients characteristics at recurrence.*

Characteristic	Number	Percentage
Patients age (years)		
≤ 65	70	67.3%
> 65	34	32.7%
PFI (months)		
≤ 6	12	11.5%
6 – 12	35	33.7%
> 12	57	54.8%
Number of recurrence site		
Single	67	64.4%
Multiple	37	35.6%
Site of recurrence		
Pelvic	11	10.6%
Abdominal	26	25.0%
RP	24	23.1%
Abdomen + pelvis and/or RP N	20	19.2%
Distant*	7	6.7%
Distant** + other sites***	16	15.3%
CA 125 at recurrence (U/ml)▲		
> 35	78	79.6%
> 46	74	75.5%
> 118	48	49.0%
> 190	25	25.5%
Treatment at recurrence		
Chemotherapy	69	66.3%
Surgery + chemotherapy	29	27.8%
Radiotherapy	1	1.0%
Surgery + radiotherapy	3	2.9%
Chemotherapy + radiotherapy	1	1.0%
Best supportive care	1	1.0%

PFI: platinum-free interval; RP: retroperitoneal; N: lymph node.
* pleura, 2; mediastinic N, 1; lung, 1; liver, 1; brain, 2;
** liver, 5; mediastinic N, 4; spleen, 3; lung, 1; brain, 1; liver + spleen, 2;
*** abdomen, 7;RP N, 6; abdomen+ pelvis, 2; pelvis + RP N, 1;
▲Data available for 98 patients.

Results

At presentation, according to the FIGO classification tumour stage was IIIa in 13 patients (12.5%), IIIb in seven (6.7%), IIIc in 76 (73.1%), and IV in eight (7.7%). Histologically, 88 (84.7%) carcinomas were serous, seven (6.7%) endometrioid, five (4.9%) mixed, two (1.9%) clear cell, one (0.9%) carcinoma was mucinous, and another one (0.9%) undifferentiated. Tumour grade was G_1 in one (0.9%) patient, G_2 in 23 (22.1%) patients, and G_3 in 80 (77.0%). After initial surgery, 32 (30.8%) patients had no macroscopic residual disease, 17 (16.3%) had macroscopic residual disease ≤ one cm, and 55 (52.9%) had a larger residual tumour. First-line chemotherapy consisted of: 1) paclitaxel 175 mg/m^2 + carboplatin AUC 5-6 every three weeks in 95 (91.4%) patients, 2) epidoxorubicin 80 mg/m^2 + paclitaxel 175 mg/m^2 + carboplatin AUC 5 every four weeks in four (3.8%), and 3) paclitaxel 175 mg/m^2 + carboplatin AUC 5 + bevacizumab 15 mg/kg every three weeks in five (4.8%). Second-look surgery was performed in 26 (25.0%) women. Consolidation treatment was given to 57 (54.8%) patients, and consisted of: 1) two to three cycles of the same induction chemotherapy in ten patients, 2) six cycles of three-weekly paclitaxel 175 mg/m^2 in 24, 3) 21 cycles of weekly paclitaxel 60 mg/m^2 in 16, 4) up to 22 cycles of three-weekly bevacizumab 15 mg/kg in five, and 5) and other agents in two.

Patient characteristics at the time of recurrence are shown in the Table 1. PFI was > 12 months in 57 (54.8%) patients, the recurrence was single in 67 (64.4%), and abdomen was the most common site of recurrence (55 patients [52.9%]: as single site in 26 patients, in association with pelvis and/or retroperitoneal nodes in 20, and in association with distant sites in nine). Treatment at recurrence consisted of chemotherapy in 69 (66.3%) women and secondary cytoreductive surgery plus chemotherapy in 29 (27.8%). Among the latter, 24 (82.8%) had no macroscopic residual

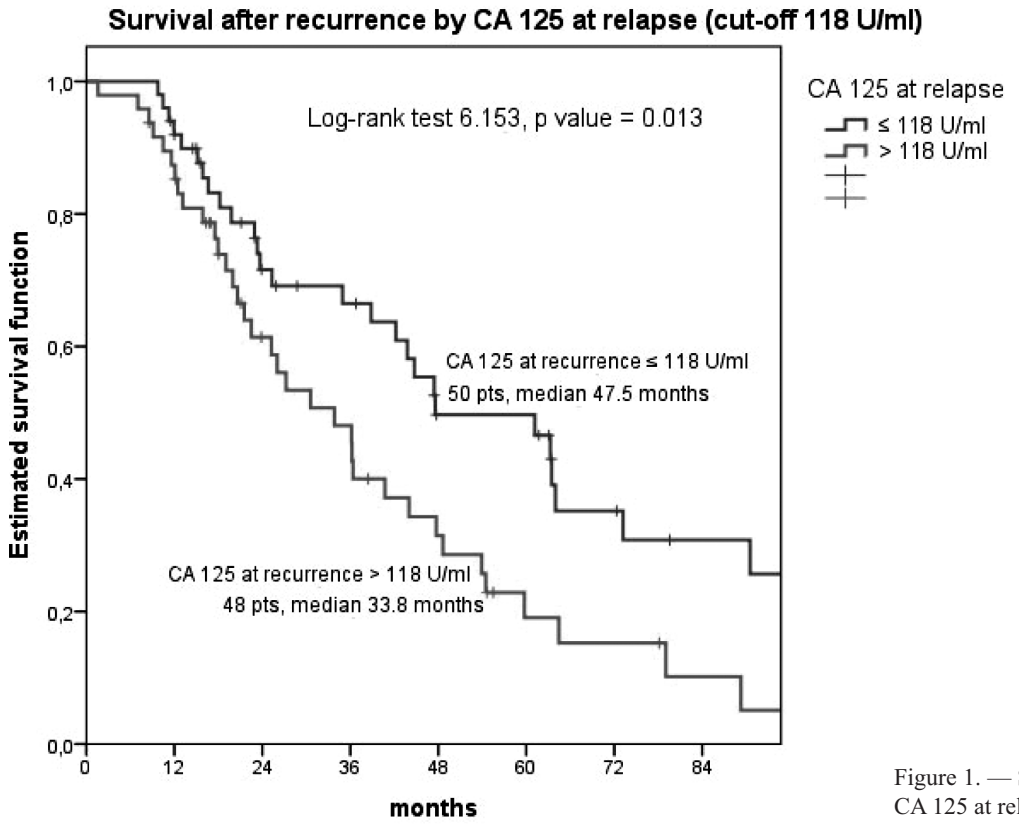

Figure 1. — Survival after recurrence by CA 125 at relapse (cut-off 118 U/ml).

disease, one (3.4%) had a macroscopic residuum < one cm, and four (13.8%) had residual disease > one cm after secondary surgery.

CA 125 levels at the time of relapse were available for 98 (94.2%) women, and ranged from 5.0 to 2,219.0 U/ml. The 25%, 50%, and 75% quantiles of serum CA 125 were 46 , 118 , and 190 U/ml, respectively. Antigen values were >35 U/ml in 78 patients (79.6%).

In the entire cohort two-, three-, five-, and seven-year survival after recurrence were 64.8%, 55.0%, 33.6%, and 21.0%, respectively. Median survival after recurrence was 38.8 months. By log-rank test, survival after recurrence was related to consolidation treatment (not performed *vs.* performed, median = 48.6 months *vs.* 34.9 months, $p = 0.046$), PFI (> 12 months *vs.* 6-12 months *vs.* < six months, median = *47.7* months *vs. 26.0* months *vs. 12.9* months, $p < 0.000005$), number of recurrence sites (single *vs.* multiple, median = 43.7 months *vs.* 33.8 months $p = 0.03$), treatment at recurrence (surgery plus chemotherapy *vs.* chemotherapy alone, median = 79.0 months *vs.* 34.9 months, $p = 0.002$), and serum CA 125 at recurrence taking 118 U/ml as cut-off (> 118 U/ml *vs.* 118 U/ml, median = 47.5 months *vs.* 33.8 months, $p = 0.013$) (Figure 1) (Table 2). On multivariate analysis (Table 3), consolidation treatment ($p = 0.007$), PFI ($p = 0.0001$), treatment at recurrence ($p = 0.01$), and serum CA 125 at recurrence taking 118 U/ml as cut-off ($p = 0.04$) were independent prognostic variables for survival after recurrence.

Discussion

Serum CA 125 assay is commonly used for the follow-up of ovarian carcinoma patients in complete response after primary treatment, but the clinical usefulness of this biochemical monitoring is still debated [24, 25]. The UK Medical Research Council and the European Organization for the Research and Treatment of Cancer entered 529 women in complete remission into a randomized trial of early chemotherapy based only on rising serum CA125, but there were no symptoms vs. delayed chemotherapy of symptomatic recurrence, regardless of CA125 levels [26]. With a median follow-up of 56.9 months, there was no difference in overall survival between early and delayed treatment (median survival = 25.7 months *vs.* 27.1 months, hazard ratio [HR] = 0.98, 95% confidence interval [CI]= 0.80−1.20, $p = 0.85$). Although this trial appeared to suggest that the routine surveillance with CA125 assay in asymptomatic patients did not offer any survival advantage, several limitations of this study must be taken into account. For instance, the role of secondary cytoreductive surgery was not considered and at the time of trial conduction more active second-line drugs/regimens were not yet available

Table 2. — *Variables predictive of survival after recurrence by univariate analysis.*

Variable	Patients	Two-year	Three-year	Five-year	Seven-year	*p* value
FIGO Stage						
IIIa-IIIb	20	73.0%	61.8%	32.7%	32.7%	0.274
IIIc-IV	84	63.0%	53.4%	34.4%	17.9%	
Histotype						
Non serous	16	73.9%	53.9%	53.9%	53.9%	0.434
Serous	88	63.3%	54.9%	30.7%	17.9%	
Tumor grade						
G_{1-2}	24	83.3%	64.9%	40.4%	28.9%	0.487
G_3	80	59.0%	52.3%	31.7%	19.0%	
RD (cm)						
0	32	71.8%	71.8%	40.6%	27.1%	
> 0-- ≤1	17	76.0%	42.2%	25.3%	12.7%	0.307
> 1	55	57.7%	49.5%	32.0%	20.3%	
Ascites						
No	51	72.4%	62.9%	39.3%	23.4%	0.346
Yes	53	57.6%	47.2%	28.3%	18.8%	
Second look						
Performed	26	79.9%	71.5%	46.2%	27.0%	0.177
Not performed	78	59.6%	49.0%	26.4%	19.8%	
Consolidation therapy						
No	47	74.8%	63.3%	44.6%	32.4%	0.046
Yes	57	57.4%	49.0%	25.2%	12.8%	
Age at recurrence (years)						
≤ 65	70	64.7%	53.9%	33.8%	17.9%	0.597
>65	34	64.9%	57.3%	34.4%	29.4%	
PFI (months)						
≤ 6	12	25.0%	12.5%	0%	0%	
6-12	35	54.5%	45.4%	31.8%	13.2%	0.000005
> 12	57	79.4%	69.3%	41.7%	29.5%	
Number of recurrent sites						
Single	67	66.4%	59.7%	39.9%	27.8%	0.03
Multiple	37	62.2%	43.6%	16.3%	0%	
Sites of single recurrence						
Pelvic	11	72.7%	72.7%	51.9%	34.6%	
Abdominal	26	60.7%	41.5%	31.2%	26.0%	0.901
Retroperitoneal N	24	70.8%	70.8%	47.0%	21.5%	
Distant	7	57.1%	57.1%	28.6%	28.6%	
Ca 125 (U/ml) at recurrence						
≤ 35	20	70.0%	65.0%	54.2%	31.6%	0.145
> 35	78	65.8%	55.1%	28.4%	16.9%	
CA 125 (U/ml) at recurrence						
≤ 46	24	69.7%	65.3%	51.3%	26.1%	0.243
> 46	74	65.6%	54.3%	28.0%	18.4%	
CA 125 (U/ml) at recurrence						
≤ 118	50	71.6%	66.5%	49.7%	30.8%	0.013
> 118	48	61.4%	48.0%	19.1%	10.2%	
CA 125 (U/ml) at recurrence						
≤ 190	73	68.7%	63.5%	38.2%	21.7%	0.305
> 190	25	60.3%	40.2%	24.1%	18.1%	
Treatment at recurrence						
Surgery + CT	29	75.3%	75.3%	66.5%	49.9%	0.002
CT alone	69	63.3%	50.0%	21.0%	12.2%	

G_1: well differentiated; G_2: moderately differentiated; G_3: poorly differentiated; RD: residual disease; rec., recurrence; PFI: platinum-free interval; N: lymph node; CT: chemotherapy.

Table 3. — *Variables predictive of survival after recurrence by multivariate analysis.*

Variable	Parameter estimated	Standard error	Wald c^2	HR	95% CI	*p* value
Consolidation treatment	0.922	0.341	7.309	2.515	1.289-4.907	0.007
PFI	0.855	0.229	13.973	2.351	1.502-3.680	0.0001
Treatment at recurrence	1.026	0.410	6.268	2.789	1.249-6.226	0.01
CA125 at recurrence (118 U/ml)	0.664	0.323	4.221	1.943	1.031-3.661	0.04

HR: hazard ratio; 95% CI: 95% confidence interval; PFI: platinum-free interval, time to recurrence; Rec: recurrence.

[27]. In the near future, the anticipation of salvage therapy will probably play a different role.

An even more debated question is the prognostic relevance of serum CA 125 levels at the time of clinical or radiological detection of recurrent ovarian carcinoma [18-22]. Makar *et al.* [18] reported that serum CA 125 was >35 U/ml in 82% of 135 patients with recurrent disease. The patients with serum CA 125 ≤ 35 U/ml had longer post-recurrence survival than those with higher antigen value ($p < 0.01$). Among these latter, no difference in survival was detected at any higher cut-off value for serum CA125.

Mahner *et al.* [20] assessed a series of patients undergoing secondary cytoreduction for recurrent disease and found that serum preoperative CA 125 was > 35 U/ml in 81% of 36 women, with a median value of 212 U/ml. However, multivariate analysis failed to detect a prognostic relevance for preoperative CA125. Berek *et al.* [21] analyzed a cohort of 145 clinically complete responders after primary treatment and found no significant survival difference between patients randomly allocated to receive maintenance immunotherapy with oregovomab or placebo. However, Cox regression analysis showed that the velocity of CA125 increase at recurrence was an independent predictor of post-relapse outcome ($p = 0.006$).

Friederick *et al.* [22] assessed 62 patients with recurrent disease undergoing secondary cytoreduction and reported that mean preoperative CA125 levels were significantly lower for the women debulked to no visible disease compared to those with ≤ one cm or > one cm macroscopic residuum (69.1 U/ml *vs.* 290.7 U/ml *vs.* 1978.4 u/ml, $p = 0.001$). A receiver operating characteristic curve revealed that a cut-off level of 250 U/ml for CA125 best predicted the chance of achieving a complete surgical cytoreduction, which was associated with a significant survival advantage.

In a previous multicenter study [19] the present authors assessed 73 patients with advanced ovarian carcinoma who were treated with surgery plus platinum-based chemotherapy between 1986 and 1992, that achieved a complete clinical response, and that subsequently developed recurrent disease. Serum CA 125 at the time of relapse was > 35 U/ml in 91.8% of the women, and the 25%, 50%, and 75% quantiles of marker levels were 76, 178, and 339 U/ml. In the 60 patients who received salvage chemotherapy with or without surgery, survival after recurrence was related to time to recurrence but not to serum CA 125 at relapse at any cut-off value for the antigen. In the present study, the authors assessed 104 patients who developed recurrent disease after the achievement of a complete clinical or pathological response following primary cytoreduction and paclitaxel- and platinum-based chemotherapy, performed between 1996 and 2013. Serum CA 125 at recurrence was > 35 U/ml in 79.6% of the patients, and the 25%, 50% and 75% quantiles of antigen values were 46, 118, and 190 U/ml, respectively. In the entire series, not only PFI but also consolidation treatment, treatment at recurrence, and serum CA 125 at recurrence taking 118 U/ml as cut-off were independent prognostic variables for further survival. Patients who recurred after consolidation treatment had a 2.515-fold higher risk of death than relapsed patients who did not receive consolidation treatment, probably because the former had a higher chance to have chemo-resistant residual clones. Patients treated with chemotherapy alone had a 2.789-fold higher risk of death than those who underwent secondary cytoreductive surgery plus chemotherapy.

A consensus regarding the role of secondary debulking surgery in recurrent ovarian carcinoma has not yet been reached, although several retrospective studies appear to suggest a survival benefit for patients with complete resection of all macroscopically detectable lesions [27-33]. Even if factors predicting optimal resectability are not yet clearly defined, the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial showed that a combination of good performance status, early FIGO stage initially or no residual tumour after first surgery, and absence of ascites could predict complete debulking in approximately 80% of the cases [30-34]. AGO DESKTOP III randomized trial is currently comparing cytoreductive surgery plus chemotherapy *vs.* chemotherapy alone in patients with platinum-sensitive recurrent ovarian carcinoma.

In the present study, serum CA 125 at the time of relapse, taking the value corresponding to the 50% quantile as cut-off, was an independent prognostic variable for clinical outcome. Patients with serum CA 125 ≥ 118 U/ml had approximately two-fold higher risk of death than those with lower antigen value, irrespective of further treatment. These results disagree with the present authors previous study. However, median survival after recurrence has improved in the last years, probably because of a greater use of secondary cytoreductive surgery with the goal to remove all

macroscopically detectable disease and a larger availability of salvage drug regimens. In the present study, 24 of the 29 patients selected for secondary debulking plus chemotherapy had no residual visible disease after surgery, and most patients that underwent chemotherapy with or without surgery received multiple chemotherapy lines during the course of the disease. Therefore, the prognostic relevance of a clinical or biological variable, such as serum CA 125 assay at recurrence, may be different from that observed in a previous group of patients less heavily treated after recurrence.

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Address reprint requests to:
A. GADDUCCI, M.D.
Department of Experimental and Clinical Medicine
Division of Gynecology and Obstetrics
University of Pisa
Via Roma 56
Pisa 56127 (Italy)
e-mail: a.gadducci@med.unipi.it