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The Clinical Value of Serum CA125 Levels in Ovarian Cancer Patients Receiving Platinum Therapy

R.G. FISH,*† M.D. SHELLEY,† T. MAUGHAN,† I. ROCKER‡ and M. ADAMS†

†*South Wales Radiotherapy and Oncology Service, Velindre Hospital, Whitchurch, Cardiff, U.K. and* ‡*The Royal Gwent Hospital, Newport, Gwent, U.K.*

Abstract—*Serum CA125 concentrations are elevated in* 60% (49/86) *of patients, with histologically proven residual adenocarcinoma of the ovary, before chemotherapy. The frequency of elevated levels correlates with stage of disease and tumour size but not histological tumour type. Serial antigen determinations in* 44 *patients receiving monthly i.v. infusions of platinum therapy suggest that an elevated serum CA125 concentration after chemotherapy may identify the presence of residual tumour but a serum antigen level falling into the normal range does not always indicate the complete eradication of tumour. The role of this serum marker is limited by lack of sensitivity for small tumour masses.*

INTRODUCTION

OVARIAN cancer presents insidiously so that many patients already have tumour spread throughout the peritoneal cavity when diagnosis is established at surgery [1]. In the majority of cases, complete removal of the tumour mass is not possible and patients with residual disease are treated with multiple courses of either a single cytotoxic drug [2] or a combination of agents [3]. The assessment of the effectiveness of chemotherapy is difficult, however, because relatively large tumour masses may not be palpable and second look laparotomy is often required to make a more reliable estimate.

Late diagnosis and the inability to assess accurately the response to chemotherapy have led to the search for serum marker substances that may be clinically useful in early diagnosis and/or monitoring disease activity during and after therapy [4–8]. One approach, using polyclonal heteroantisera [9] and more recently monoclonal antibodies [10, 11], has been to detect ovarian tumour associated antigens, apparently expressed on the cell surface and shed or secreted by tumour cells into the circulation.

In 1983, Bast *et al.* described a potentially useful serum immunoradiometric assay [12] that detects a glycoprotein antigen (CA125) derived from a human ovarian tumour cell line [13]. A monoclonal antibody to this antigen was produced using a mouse somatic cell hybridization technique. These workers showed that increased serum antigen levels above the limits of the normal range for healthy subjects were found in 82% of women with epithelial ovarian cancer and sequential determinations suggested that serum CA125 levels may aid in diagnosis and in monitoring the course of the disease [12, 14].

The present study was designed (a) to establish the relationships between serum CA125 levels, stage of disease, tumour size and histological tumour type in patients with residual adenocarcinoma of the ovary and (b) to determine the clinical usefulness of this proposed serum test in the assessment of patients' response to platinum therapy. The results suggest that elevated serum CA125 concentrations during and after chemotherapy identifies the presence of residual tumour in a number of patients but a serum antigen level falling into the normal range does not always indicate the eradication of tumour.

MATERIALS AND METHODS

Clinical data

Serum was obtained from 72 apparently healthy females of mean age 36 years (range 22–64), 23 patients with benign gynaecological conditions (6 benign cysts, 10 fibroids, 7 dysfunctional bleeding) and 3–4 weeks post-operatively from 86 patients (mean age 55 years, range 34–73) diagnosed at laparotomy as having adenocarcinoma of the ovary.

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*To whom correspondence and requests for reprints should be addressed.

Table 1. Percentage of patients with elevated serum CA125 before chemotherapy, correlated with stage of disease, tumour size and histology

	No. of cases	Patients with elevated CA125 levels* (%)
Apparently healthy females	72	
Benign gynaecological conditions	23	
Ovarian cancer (post-laparotomy)	86	49 (57)
FIGO stage of disease		
IIB	15	3 (20)
III	54	32 (59)
IV	17	14 (82)
Maximum residual tumour nodule diameter (cm) at 1st laparotomy		
< 2	32	12 (38)
2–10	26	13 (50)
> 10	28	24 (86)
Histological type		
Serous	43	25 (58)
Undifferentiated	22	16 (73)
Mucinous	7	2
Endometrioid	9	3
Clear cell	2	2
Mixed	3	1

*Serum CA125, > 35 units/ml.

All patients were classified according to histological type, residual tumour size after 1st laparotomy and FIGO stage (Table 1). The maximum size and distribution of residual tumour nodules were assessed at first surgery and post-operatively by clinical and ultrasound examination where appropriate. The majority of patients received an intravenous infusion of *cis*-diamminedichloroplatinum (cisplatin 100 mg/m^2/6 hr). The cisplatin analogue, *cis*-diammine-1,1-cyclobutanedicarboxylate platinum (carboplatin 400 mg/m^2/30 min) was given to four patients. Treatment was repeated every 4 weeks. During chemotherapy, tumour response was assessed monthly by pelvic and abdominal examination and ultrasound measurements. Of the 44 patients in whom serial samples were estimated, 17 patients had no palpable or radiologically detectable tumour (NED, $n = 17$) before and after completing up to five courses of platinum therapy. The remaining 27 patients with detectable disease after primary laparotomy were classified according to clinical and ultrasound examination when they had received up to five courses of platinum. In seven patients the tumour mass progressed and showed less than 50% reduction in diameter and these subjects were classified as non-responders (NR, $n = 7$). Eight patients had a greater than 50% reduction in tumour diameter and were classified as partial responders (PR, $n = 8$). In 12 patients, complete resolution of the assessable tumour occurred and these were classified as complete clinical responders (CCR, $n = 12$). These 12 patients and the 17 with no detectable disease were subjected to a second-look laparotomy 4–6 weeks after chemotherapy. At operation, the size of residual tumour nodules were measured and those patients having no macroscopic tumour had multiple biopsies taken at the site of the original disease and peritoneal fluid was taken for cytology. Thirteen of the 29 patients had visible macroscopic residual tumour confirmed by biopsy (Res., $n = 13$). Six had no macroscopic disease, but multiple biopsies with peritoneal cytology revealed histological evidence of microscopic residual tumour (PCR^+, $n = 6$). Ten patients had no evidence of macroscopic or microscopic disease (PCR^-).

Blood sampling

Blood samples from 44 patients were collected before, at monthly intervals during platinum therapy, at the end of treatment and at follow-up. Aliquots of sera were stored at −20°C. Each aliquot was thawed only once for use in this study and analyses of the serial samples of a single patient were carried out simultaneously.

CA125 assay

Tumour antigen concentration in serum was measured using an immunoradiometric assay (ELSA) available from International-CIS (U.K.), London. The assay uses a solid phase radioimmune absorbant, coated with an anti-CA125 mouse monoclonal antibody, OC 125. When ^{125}I-labelled antibody is incubated with serum containing the ovarian antigen, the CA125 present binds simultaneously to the solid phase and the labelled antibody. After washing the tubes, the measured

radioactivity associated with the solid phase is proportional to the concentration of CA125 in the sample. The intra and inter assay precisions ($n = 6$) of patients sera at an antigen level of 90 units/ml were 6.3 and 11.3%, respectively [15].

RESULTS

Before chemotherapy

In 72 apparently healthy females and 23 patients with benign gynaecological conditions, the maximum serum CA125 concentration achieved was 20 units/ml. The upper limit of normal was arbitrarily taken as 35 units/ml as suggested by the originators of the test [12]. Forty-nine of 86 patients with residual ovarian cancer before chemotherapy had a serum antigen level above the upper limits of normal. The frequency of elevated levels correlated with stage of disease and maximum tumour nodule diameter after 1st surgery but was independent of histological tumour type (Table 1). The mean serum CA125 levels (± SD) in patients with tumour masses < 2 cm, 2–10 cm and > 10 cm were 118 ± 41, 93 ± 38 and 394 ± 81 units/ml, respectively. No significant difference in the mean serum antigen level was observed between the two groups of patients with tumour masses < 2 cm and 2–10 cm, but analysis of variance showed a highly significant difference between both these groups when compared with patients classified in the large (> 10 cm) tumour group ($P < 0.001$).

Serial monitoring

Of the 44 patients from whom serial blood samples were obtained 26 had an elevated pre-chemotherapy serum CA125 level. Two of the 18 patients, who had serum antigen levels initially in the normal range, developed elevated levels by the end of the platinum courses in association with progression of clinical disease (patients 7 and 23, Table 2). The initial clinical characteristics, response to cytotoxic drug therapy, 2nd look laparotomy findings, and the serum CA125 levels before and after platinum therapy in these 28 patients are shown in Table 2.

In seven patients who did not respond to therapy and 5/7 patients who had a partial tumour response, the serum CA125 concentration remained above the upper limits of normal at the end of the platinum courses. In two patients, who had a partial tumour response, the serum antigen level had fallen into the normal range by the end of platinum therapy. The remaining 14 patients had a second look laparotomy. At the end of platinum therapy, eight of these patients had an elevated serum antigen level and this correlated with the presence of tumour at second look surgery in every case. Of the six patients with normal CA125 levels before second look laparatomy, four had residual disease and two were histologically disease free as shown by negative biopsies and negative peritoneal cytology.

Serum CA125 measurements taken after the third platinum infusion were compared with pre-chemotherapy antigen levels. In eight patients, the serum CA125 level remained elevated (± 10% of initial value) or had increased above the initial value and in this group of patients the clinical findings were; NR ($n = 6$) and a PR in two patients (1–8, Table 2). The serum antigen levels were either in the normal range or had fallen by at least 10% after three platinum courses in the remaining patients. The clinical assessment in these individuals was, NR ($n = 1$), PR ($n = 5$), CCR ($n = 7$) and NED ($n = 7$).

Examples of the serum CA125 profiles during chemotherapy and at follow-up in four patients are shown in Fig. 1. Patient 9 had a partial clinical response to cisplatin therapy and at follow-up the disease progressed rapidly. The serum antigen level in this patient increased during the platinum courses and remained elevated throughout the follow-up period. The patient died at 28 months with clinical evidence of progressive disease. Constantly elevated CA125 levels were observed over 18 months in patient 16 who had a complete clinical response to cisplatin therapy but residual tumour at second look laparotomy, and subsequently died of progressive disease at 31 months. Patient 21 had a complete clinical response to cisplatin therapy but at second look laparotomy, residual disease was present. Regression of tumour again occurred after five courses of carboplatin, but this patient, although still alive, has progressive disease at 18 months. The serum CA125 levels in patient 21 followed the clinical course of the disease but after both platinum analogue courses, the antigen concentration had fallen into the normal range, despite the presence of residual tumour. During cisplatin therapy, the serum antigen levels decreased into the normal range in patient 28 and CA125 concentration remained low for a 12-month follow-up period. This patient, who was not clinically evaluable during chemotherapy (< 2 cm mass) had no histological evidence of disease at second look laparotomy and has no palpable tumour after 1 year.

DISCUSSION

This study confirms a previous investigation [16] that elevated serum CA125 levels before chemotherapy correlate with tumour burden and applies to all histological types of epithelial cancer, including mucinous tumours which have been reported as negative [12, 17]. This discrepancy is not surprising since the pathological differentiation of mucinous from endometrioid tumours is known to be difficult [18]. Elevated serum antigen levels occur, less fre-

Table 2. Serum CA125 levels in 28 patients before and at the end of platinum therapy

Case No.	Age	Stage	Histology	Tumour size (cm)	CA125 before drug therapy*	Clinical response†	CA125 end of drug therapy*	SLO findings‡
1	56	IV	Serous	> 10	794	None	880	—
2	60	III	Serous	> 10	425	None	750	—
3	62	III	Undiff.	> 10	632	None	626	—
4	57	III	Serous	> 10	560	None	365	—
5	68	III	Mucinous	2–10	99	None	144	—
6	53	IV	Mucinous	2–10	42	None	60	—
7	38	III	Endometrioid	2–10	14	None	42	—
8	40	III	Serous	> 10	1311	PR	1281	—
9	62	IIB	Undiff.	> 10	286	PR	940	—
10	53	IV	Serous	> 10	180	PR	105	—
11	62	IIB	Serous	> 10	226	PR	47	—
12	61	IV	Serous	2–10	230	PR	385	—
13	63	III	Serous	> 10	500	PR	17	—
14	59	III	Undiff.	2–10	120	PR	6	—
15	48	IV	Undiff.	> 10	113	CR	73	Res.
16	40	IV	Serous	> 10	135	CR	100	Res.
17	56	III	Serous	> 10	203	CR	108	Res.
18	62	III	Undiff.	> 10	239	CR	77	Res.
19	36	III	Endometrioid	> 10	140	CR	135	CR+
20	57	IV	Undiff.	> 10	450	CR	30	Res.
21	49	IV	Undiff.	2–10	420	CR	15	Res.
22	44	III	Endometrioid	< 2	175	NED	100	Res.
23	65	III	Serous	< 2	10	NED	55	Res.
24	69	III	Serous	< 2	500	NED	10	Res.
25	34	III	Serous	< 2	107	NED	60	CR+
26	54	III	Serous	< 2	500	NED	15	CR+
27	64	III	Undiff.	< 2	380	NED	35	CR−
28	61	IIC	Undiff.	< 2	60	NED	6	CR−

*Arbitrary units/ml.
†None, progressive or static disease; PR, partial response; CR, complete response; NED, no evaluable disease.
‡Res., macroscopic residual disease; CR+, microscopic disease; CR− no histological evidence of disease at second-look operation (SLO).

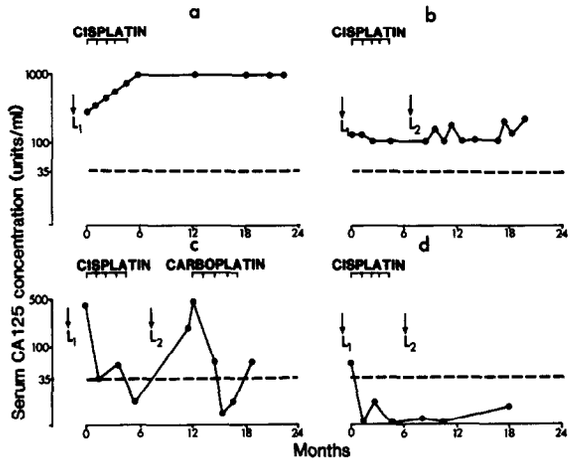

Fig. 1. Sequential serum CA125 levels in four patients receiving cisplatin or carboplatin. Dotted line represents upper limit of normal range (35 units/ml). *L1 and L2 indicate first and second laparotomy, respectively.* (a) *Patient* 9 *had a partial response followed by progressive disease.* (b) *Patient* 16 *had a complete clinical response (CR) but residual tumour at L2.* (c) *Patient* 21 *had a CR to cisplatin but residual disease at L2 and a partial tumour regression during carboplatin therapy.* (d) *Patient* 28 *was NED during cisplatin therapy; had no histological evidence of disease at L2 and has no palpable tumour after a* 12*-month follow-up period.*

quently, in patients with adenocarcinoma of the colon, breast and cervix [12, 16], hepatoma, liver metastases, peritonitis, chronic liver disease and acute pancreatitis [19], thereby imposing limitations on its use in screening for and diagnosis of ovarian cancer.

Persistently elevated or rising serum antigen levels during therapy appears to identify patients who are not responding to cytotoxic drug treatment (Table 2). Also, in this study, elevated or rising levels of serum CA125 at the end of chemotherapy are associated with the presence of residual disease, even when patients are classified as complete responders [12, 16, 20].

This investigation and others [12, 16, 20–22] have shown that the serum obtained from approximately one third of patients, with residual adenocarcinoma of the ovary before chemotherapy, do not have elevated CA125 concentrations and suggests the need to study tumour markers [23–25] that could be used in conjunction with CA125 in this particular group of patients.

It would appear that serial monitoring with CA125 offers a further means of assessing response to chemotherapy but its role is limited by lack of sensitivity for small tumour masses.

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