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Early Serum CA125 Response and Outcome in Epithelial Ovarian Cancer

Charles W.E. Redman, George R. Blackledge, Krystyna Kelly, Judith Powell, Edward J. Buxton and David M. Luesley

The prognostic value of serum CA125 levels before and after two courses of chemotherapy was assessed in 50 patients with advanced epithelial ovarian cancer. Patients with serum CA125 values below 35 U/ml after two courses were significantly more likely to achieve complete remission and had a significantly longer median survival. In multivariate analysis, serum CA125 levels after two courses were the most important independent prognostic factor: it was possible to predict survival status at 12 months with an overall accuracy of 93%. Serum CA125 can be used to evaluate quantitatively chemotherapeutic response and at an early stage classify patients into good and poor risk groups. Such an approach would facilitate the selection of appropriate therapy and could reduce toxicity.
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INTRODUCTION

SERUM CA125 has been extensively studied in relation to the management of ovarian cancer [1–3]. Initial studies evaluated the correlation with observed response [4, 5], although false negatives in small volume disease are a problem. Used in this way CA125 assay has little value other than sparing some patients second-look surgery, which is itself questionable [6]. Several studies have evaluated early CA125 response to predict outcome [7–9]. Van der Burg *et al.* [9], using serial measurements, reported that patients with a CA125 half-life of less than 20 days had a significantly longer median survival compared with patients with a longer half-life. However, 40% (approximately half of which had FIGO stage I disease) of the study group had no macroscopic postoperative disease and these findings are not necessarily relevant to patients with residual disease. Lavin *et al.* [7] correlated serum CA125 levels at 3 months with response at second-look surgery: all patients with levels greater than

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35 U/ml had persistent disease compared with 5 of 14 patients with negative levels, i.e. less than 35 U/ml, survival was not analysed. We have assessed the prognostic value of early serum CA125 values in patients with advanced epithelial ovarian cancer (EOC) to identify those patients who would or would not derive significant benefit from intensive first-line therapy.

PATIENTS AND METHODS

Patients

Between March 1986 and March 1988, CA125 was measured serially in 76 EOC patients managed by the West Midlands Ovarian Cancer Group. 26 patients were excluded: 18 did not have both a pretreatment sample and one taken after two courses of chemotherapy and 6 patients had no postoperative disease (5 stage I and 1 patient with stage III disease).

50 patients (Table 1) with macroscopic residual disease had CA125 measured before treatment and before the third course of treatment. The amount of postoperative disease was as recorded at the end of surgery, rather than at the time of start of treatment (median 5 weeks after primary surgery). All patients received primary chemotherapy following first-line surgery.

Table 1. Characteristics of study group

Mean age (95% CI)	56.5 (51.7 to 60.8)
FIGO stage	
II	3
III	37
IV	10
Bulk of disease (cm)	
< 2	22
2–5	19
5–10	6
> 10	3
Histological type	
Serous	29
Mucinous	5
Endometroid	11
Clear	3
Anaplastic	2
Histological grade	
Well	11
Moderate	20
Poor	17
Unspecified	2
Overall response	
Complete response	27
Partial response	4
Static	1
Progression	8
Not evaluable	10
Initial serum CA125 (U/ml)	
< 35	7
> 35	43
Second serum CA125 (U/ml)	
< 35	27
> 35	23
Chemotherapy	
Cisplatin/cyclophosphamide	28
Cisplatin/bleomycin/doxorubicin	18
Cisplatin/mitoxantrone	4

Table 2. CA125 levels (U/ml) before and after two courses of treatment according to response in evaluable patients*

	Responders (n = 31)			Non-responders (n = 9)			
Time	Mean	Range	S.D.	Mean	Range	S.D.	P
Pre-treatment	295	14–1356	309	473	116–1813	536	0.06
After two courses	45	6–482	93	462	40–490	333	0.0001

*Responders = complete and partial response. Non-response = static response and progression.

Staging was done according to the International Federation of Obstetrics and Gynaecology classification. Histological assessment was centrally reviewed with World Health Organization criteria [10]. All patients received cisplatin-based chemotherapy every 21 days. These combination regimens all included cisplatin 75 mg/m^2 with either cyclophosphamide 750 mg/m^2 or doxorubicin 50 mg/m^2 and bleomycin 15 mg/m^2, or mitoxantrone 14 mg/m^2. The overall response rate in evaluable patients was 77% (International Union Against Cancer [UICC] criteria); 10 patients with small volume residual disease could not be evaluated. The median survival for the study group was 16.4 months (95% confidence limits [CI] 9.8 to 23.0). Median time on study was 25 months (95% CI 23 to 27; range 14–32).

Serum samples

Pre-operative serum CA125 levels were not available. Serum CA125 levels were assayed in serum specimens obtained immediately before the first course of chemotherapy, a median of 36 (95% CI 25 to 47) days from primary surgery, and 3 weeks after the second course of treatment, a median time from the first sample of 65 (63 to 67) days.

CA125 was assayed with CIS kit according to the manufacturer's instructions. Samples were stored at −20°C until assayed with kits with different batch numbers. The inter-assay coefficient of variation in eighteen runs with the provided internal control (mean 121 U/ml) was 8%.

Statistical methods

Analysis of variance was used to analyse the association of serum CA125 with disease bulk. Natural logarithmic transformation of serum CA125 data was used to normalize its positively skewed distribution. A t test was used to compare sample groups (after transformation if required). χ^2 with Yates' correction was used to analyse discontinuous data. Initial univariate analysis of potential prognostic variables, including serum CA125 values at the start of treatment and after two courses, and percentage changes (25, 30, 40, 50, 60, 70, 80, 86, 90, 95) was done with Kaplan–Meier curves and the differences between the groups tested with the log-rank test. Serum CA125 was analysed both as a continuous variable and as a discontinuous variable with a cut-off of 35 U/ml [1]. To determine the independent effect of individual prognostic factors, discriminant analysis was done with survival at 12 months after primary surgery as the endpoint. This time point was chosen since patients who died within 12 months of primary surgery can be described as a poor risk

Table 3. Results of log-rank tests for on-study prognostic variables that were included in discriminant analysis

Variable	Total	Dead	% survival at 12 mo	χ^2	P
FIGO stage					
II	3	1	100		
III	37	24	76	1.74	0.42
IV	10	8	70		
Histological type					
Serous	29	21	79.3	0.27	0.60
Rest	21	12	71.4		
Mucinous	5	1	100	3.5	0.06
Rest	45	32	73.3		
Histological grade					
Well	11	6	72.7	0.50	0.48
Rest	39	27	76.9		
Poor	17	11	70.6	0.08	0.78
Rest	33	22	78.8		
Bulk of residuum					
< 2 cm	22	9	90.9	7.02	0.008
> 2 cm	28	24	64.2		
Initial serum CA125					
>35	43	32	72.7	7.04	0.008
<35	7	1	100		
Second serum CA125					
>35	27	14	47.8	11.12	0.0009
<35	23	19	100		
Fall in serum CA125*					
< 30%	13	9	46.1	1.33	0.24
> 30%	37	24	86.5		

*The most discriminant change.

group. Several transformations of the initial and second CA125 values were used, as well as of the cut-off and various sizes of fall in CA125 values (25%, 80%, 86%, 90%). To compare the prognostic value of early serum CA125 levels with observed overall clinical response a second discriminant analysis was done including only patients with evaluable disease.

RESULTS

The mean pretreatment serum CA125 (321 U/ml, S.D. 367) was significantly higher ($P < 0.0001$) than that after two courses of chemotherapy (124 U/ml, S.D. 222). There was a significant difference in the serum CA125 levels between responding and non-responding patients after two courses (Table 2).

Univariate analysis (Table 3)

The amount of residual disease (diameter greater or less than 2 cm) and serum CA125 levels were the only significant pretreatment prognostic factors. Whilst there was an association between serum CA125 levels and the amount of residual disease ($P = 0.04$), pretreatment serum CA125 levels did have an independent prognostic value (Cox's proportional hazards model, $P = 0.03$).

Patients with serum CA125 levels less than or equal to 35 U/ml after two courses of treatment (median survival 24.2 months, 95% CI 22.1 to 26.2) were more likely to achieve complete remission ($P < 0.0001$) and had a better prognosis ($P = 0.0009$) than patients with levels greater than 35 U/ml (median survival

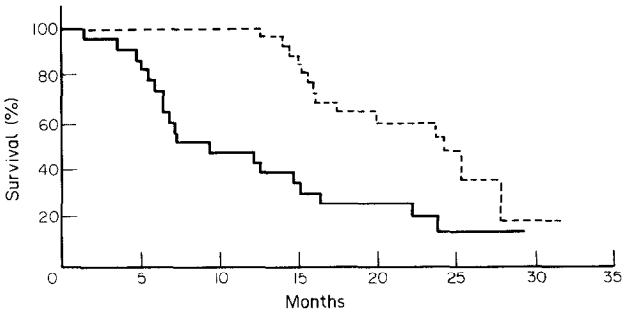

Fig. 1. Survival based on serum CA125 levels after two courses of treatment. Solid line = 35 U/ml or more, broken line = 35 U/ml or less. Significant difference in survival ($P = 0.0008$).

9.2 months, 95% CI −2.1 to 20.6) (Fig. 1). The percentage fall in serum CA125 between the first and second samples had no prognostic value.

Stepwise discriminant analysis (Table 4)

Serum CA125 after two courses gave the greatest discrimination between patients alive at 12 months and those who did not survive that long. No other variables could improve the discrimination between survivors and non-survivors. With the classification function derived from this analysis, it is possible to predict correctly outcome in 93% of patients (96% [44/46] correctly predicted to be alive at 12 months and 85% [11/13] correctly predicted to be dead). In comparison, the overall predictive accuracy of pretreatment CA125 (with the most discriminant cut-off of 100 U/ml) was 52%.

DISCUSSION

This study was primarily concerned with the prediction of short-term therapeutic benefit from potentially toxic treatment, which is of value since current therapy has resulted in little significant improvement in long-term survival in patients with advanced ovarian cancer. In this context survival status at 12 months is a reasonable end-point. At present the postoperative management of EOC is largely determined by factors such as stage, residual disease status, age and general condition of the patient [11]. These factors give an overall assessment of prognosis but little information of the likelihood of any given patient deriving useful (if only palliative) benefit from therapy.

We found that serum CA125 can be used to identify accurately good and poor risk EOC patients after only two courses of therapy and is more accurate than pretreatment CA125 levels and the size of their fall after two courses. On the basis of our

Table 4. On-study prognostic variables used in discriminant function analysis

Variable	Forms tested in discriminant analysis
Age	Age; age^2; square root of age
FIGO stage	Stage I/II vs. III/IV
Histological type	Serous vs. rest; mucinous vs. rest
Histological grade	Well vs. rest; poor vs. rest
Bulk of residual disease	<2 vs. >2 cm
Serum CA125	Serum CA125; $\log_e$ (serum CA125)
Second serum CA125	Serum CA125; $\log_e$ (serum CA125)
% fall in serum CA125	Continuous and with cut-offs at 30 and 80%

study, patients with CA125 levels greater than 35 U/ml after two courses of treatment have a mortality at 12 months of 85%. In such patients, the use of further active therapy is questionable and the identification of this subgroup would reduce unwarranted toxicity. It is possible that CA125 levels at an earlier point, such as after only one course of treatment, may yield equally useful but more timely information.

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Interferon-related Mental Deterioration and Behavioral Changes in Patients with Renal Cell Carcinoma

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Five out of 38 patients (13%) with metastatic renal cell carcinoma had mental deterioration 3 weeks to 13 months after the start of treatment with recombinant interferon alpha-C. Metastatic spread to the brain, paraneoplastic effect of the tumor on the central nervous system and other causes of dementia were excluded. Computed tomography of the brain in these patients was normal and the width of the cerebral sulci and ventricles did not correlate with the severity of dementia. Specific patterns of atrophy were not seen. General deterioration, assessed by the change in Karnofsky performance status, was associated with dementia. The dementia may have been caused by a neurotoxic effect of interferon.
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INTRODUCTION

MENTAL DETERIORATION in patients with cancer constitutes a diagnostic challenge since it may be due to different etiologies and has a major impact on further treatment planning. Various etiologies underlie the appearance of dementia and behavioral changes in these patients, such as metabolic derangements, paraneoplastic phenomena, metastatic spread to the brain, and iatrogenic causes, including damage following radiation, chemotherapy and interferon therapy [1–6]. The diagnostic approach to define the exact etiology in the complex cancer patient may be difficult. Imaging is helpful in differentiating between the various causes of dementia [7–11]. We present five patients with metastatic renal cell carcinoma (RCC) treated by recombinant interferon alpha-C who deteriorated mentally while being treated.

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PATIENTS AND METHODS

Patient population

Thirty-eight patients with metastatic RCC with no apparent mental or behavioral derangement were treated with recombinant interferon alpha-C (highly purified bacteria-derived inter-