Does the nadir CA125 concentration predict a long-term outcome after chemotherapy for carcinoma of the ovary?

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The tumour marker CA125 is an important indicator of the clinical progress of women with carcinoma of the ovary. We have investigated the interval from the nadir CA125 value to progression defined by rising CA125 (time to biochemical progression, TBP), and overall survival of patients treated with chemotherapy for this disease in relation to the nadir CA125 value in patients in whom this was <30 U/ml following chemotherapy. The median TBP in group A (38 patients, nadir ≤10 U/ml) was 2436 days, in group B (32 patients, nadir 11–20) 182 days and in group C (nine patients, nadir 21–30) 90 days, \( P < 0.001 \). This was associated with similar differences for overall survival, the median was 2968 days in group A, 537 days in group B and 537 days in group C, \( P < 0.001 \). Variations in the CA125 value even within the normal range carry useful information. This prognostic indicator will be useful in studying the management of patients following response to first-line chemotherapy.

Key words: CA125, carcinoma of the ovary, prognosis, response to chemotherapy, tumour markers

Introduction

Epithelial carcinoma of the ovary remains a disease that proves fatal to the majority of patients, but where chemotherapy has been established as a treatment that improves survival. A minority of patients attain long survival after such treatment. In recent years, the CA125 concentration has been established as a valuable tool in the diagnosis of the disease, prognosis and monitoring of treatment [1]. It is possible to identify patients whose disease is progressing after treatment by serial measurements of CA125 [2]. The value of this in instituting earlier treatment of relapse is currently under investigation. A study conducted by the Medical Research Council in the UK concluded that the level of CA125 at the third course of chemotherapy carried the greatest prognostic significance of any measurement of this substance [3].

Commercially available automated assays for CA125 are widely available. The reference range quoted is usually 0 to 35 U/ml; values within this range are considered normal and their sustained attainment is regarded as a complete biochemical response to chemotherapy. Prompted by the impression that variations within the normal range had a bearing on patient outcome, a retrospective analysis has been conducted of patients treated for ovarian cancer who have attained a complete biochemical response.

Patients and methods

From a database of CA125 values from 106 patients who were treated with chemotherapy for epithelial ovarian cancer of FIGO stage Ic–IV, the records of 79 patients who attained levels below 30 U/ml were scrutinised. Serial measurements of CA125 had been made before each cycle of chemotherapy throughout their treatment. During follow-up, this measurement was made every 5–6 weeks in the first year, every 2 months in the second year and every 3 months in the third year. After this point, measurements were made every 4–6 months. Further measurements were made if there was any reason to suspect progression. These patients were diagnosed between 1988 and 2000, and so a variety of treatments have been used. Patients from the earlier part of the period were treated with cisplatin and cyclophosphamide or single-agent carboplatin, with the introduction of paclitaxel and docetaxel in the later period. Many patients have been included in clinical trials of chemotherapy. Thirty of the 79 patients had received a taxane.

All have been treated at one institution under the care of one physician. The nadir value of CA125 was categorised into three arbitrary groups: group A, ≤10 U/ml, group B, 11–20 U/ml, group C, 21–30 U/ml. Patients were categorised into a particular group by having two consecutive samples within the stated range and the date of attainment of the nadir was defined as the date of the second sample. Biochemical progression was defined as the occurrence of a value greater than 60 U/ml that was confirmed by a subsequent value greater than 60 U/ml, the first date defining the date of progression [4]. The time to biochemical progression (TBP) was defined as the interval between the nadir and progression, and overall survival was calculated from the date of the nadir.

Assays were conducted in the Airedale General Hospital Pathology Laboratory. An Abbott Laboratories IMX system was used before 1996. After that date, an Assym analyser from the same manufacturer was used. The manufacturer’s reagents were used with standard quality...
control procedures to ensure comparability. The upper limit of normal was 35 IU/ml.

The CA125 value at the time of the third cycle of treatment was recorded as a potential correlate of prognosis [3], as was the fact that a patient had received a taxane as part of her chemotherapy or not. Standard Kaplan–Meier methods were used to plot the survival of members of each of the nadir groups and to plot the survival of patients categorised by their CA125 value at the time of the third cycle of treatment. The statistical significance of differences between the curves was tested by the log rank method and the relative contribution of the different potential correlates of prognosis was assessed by the Cox proportional hazards method.

**Results**

There were 38 patients in group A (nadir ≤10 U/ml). Six had CA125 levels in that range at the start of treatment and six attained the nadir a median of 77 days after chemotherapy was completed. The others attained their nadir during chemotherapy. Two of 32 patients in group B started chemotherapy with CA125 values in their nadir range of 11–20 U/ml; three attained their nadir 21, 98 and 153 days after the end of chemotherapy. In one patient in this group the CA125 level started to rise before first-line chemotherapy was completed. Of nine patients in group C, two had an increase in the CA125 level before treatment was completed and two attained their nadir value 80 and 90 days after this point. All other patients attained their nadir during chemotherapy.

The TBP of the three groups can be seen in Figure 1 and the overall survival in Figure 2. The median TBP in group A was 2436 days, in group B 182 days and in group C 90 days, ($\chi^2 = 39.52, 38.20, df = 2, P < 0.001$). The median survival was 2968 days in group A, 537 days in group B and 537 days in group C, ($\chi^2 = 21.76, df = 2, P < 0.001$). The differences between the curves are statistically highly significant and the overall survival of patients in group A with very low values of CA125 is highly significantly greater than that of patients in groups B and C.

Figure 3 shows that the TBP of 65 patients grouped according to whether their CA125 concentration was greater than 70 U/ml or not shows a statistically significant advantage to the 53 patients with lower values, with a median TBP of 833 days compared with 91 days for patients with higher levels ($\chi^2 = 15.52, 13.84, df = 1, P < 0.001$). However, there were only 12 patients in this group. This is because many patients whose value was above 70 U/ml at course 3 did not meet the inclusion criterion (a nadir CA125 of ≤30 U/ml) for this study.

In the Cox’s proportional hazards model, the nadir group was the most important predictor of the TBP (coefficient 0.1336, $P < 0.001$). The CA125 value at course 3, included as a continuous variable, was also a predictor of time to biochemical progression (coefficient 0.0038, $P = 0.0015$). The inclusion of a taxane in chemotherapy produced no advantage (median TBP with a taxane 256 days, with no taxane 310 days; Cox coefficient $-0.1552, P = 0.65$). The nadir group was the only predictor of overall survival that remained very highly significant ($P < 0.001$) after the effect of the other factors was allowed for.

**Discussion**

The population-derived range for CA125 in normal people ranges up to 35 U/ml in commercial assays. The detection of this antigen in the serum reflects not only neoplasms that produce an excess, but also production by normal tissues that
may vary from time to time and may be provoked by other conditions, including peritoneal surgery [5]. This study is the first to analyse a series of data which shows that values within that normal range convey important biochemical information about ovarian carcinoma. It was conducted solely in patients who had attained values well within the accepted normal range during or following their treatment. In this series, prolonged survival is primarily a characteristic of patients whose nadir value is less than 10 U/ml and those who fail to attain this level are virtually all destined to progress, the majority of them within a few months of attaining their nadir. We have used a biochemical definition of early progression and our database did not allow us to relate this to radiological or clinical progression of the tumour. However, its validity is emphasised by the poor overall survival of patients in groups B and C. The findings add to those of Bese and colleagues, who found that a cut-off value of 20 U/ml was a better predictor of the findings at second-look surgery than one of 35 U/ml [6].

The attainment of a value less than 70 U/ml at the time of the third cycle of treatment has previously been proposed as the optimal prognostic indicator based on CA125 and this may very well be the case for the interim assessment of patients during treatment [3]. Confirmation of the findings of the present study would establish that a separate assessment of prognosis following the completion of treatment has an important value. This would add to the information available to plan management. It is recognised that when platinum-based treatment is used, which is accepted as the optimal standard for chemotherapy in ovarian cancer, progression of the disease within 6 months is evidence of resistance to these drugs. Platinum compounds are unlikely to be successful in second-line therapy in these patients. The nadir CA125 value appears from the present data to be an early indicator of this situation.

Drugs in the taxane group are accepted as important components in the chemotherapy for ovarian cancer [7]. Controversy exists over their use in first-line or subsequent chemotherapy. This study does not address whether or not taxanes induce low CA125 values in more patients than other platinum-based chemotherapy but it does suggest that once an optimal CA125 response has been attained, they do not add to the durability of that response.

Maintenance paclitaxel chemotherapy has been explored in ovarian cancer [8]. New developments may include biologically targeted treatments that are used chronically as maintenance therapy. The nadir CA125 value would seem to be an important way to stratify these patients according to their risk of progression in clinical trials evaluating such agents.

The early detection of ovarian cancer is also an important area given the problems of treating advanced disease. The concentration of substances in the serum may assist in the detection of tumours; CA125 has been used in screening studies, but its sensitivity and specificity are poor. This demonstration that values within the normal range convey information about ovarian cancer may be used to increase the sensitivity of this assessment, especially if lower values are used as the starting point for longitudinal measurements [9].

This study is based on a relatively small series of data. The three categories defined were adopted simply on the grounds of numerical convenience and are not derived specifically from the characteristics of this database, so they may well be robust but need to be validated against other databases. One such study has supported their use [10]. The difference in biochemical progression between groups B and C must in part reflect the fact that a smaller proportion of increase is required to define biochemical progression from values in group C than in Group B which therefore takes less time, in other words it is a lead-time effect. For the majority of patients in group A it seems that the low values imply biological difference rather than there being an artefact of the same rate of tumour growth.

The hypotheses generated by this study require confirmation in larger series. Analyses are in progress to validate the principle observations and to investigate whether there is an optimal cut-off value or values. This is being undertaken in a large clinical trial database that will enable the relationship of the CA125 nadir to both anatomical and biochemical definitions of disease progression.

The present data add to understanding of the value of CA125 in documenting the course of patients with ovarian cancer. They show that values within the normal range convey important information about the tumour in that patients with a value greater than 10 U/ml have a very high risk of progression within the first year of diagnosis but values less than 10 U/ml imply that the patient may have an excellent outcome.

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