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Savings Obtained by CA-125 Measurements during Therapy for Ovarian Carcinoma

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The value of serial CA-125 measurements for predicting progression of ovarian carcinoma during therapy was calculated in 71 patients. The optimal algorithm that defined disease progression by CA-125 levels was either two values above 100 U/ml which had decreased by less than 50% over a minimum of 56 days, or a rise of 25% between successive samples plus a confirmatory sample. Of 13 patients with progressive disease according to the CA-125 criteria, 12 developed clinical evidence of progression within 12 months; predictions were false positive in 1, true negative in 50 and false negative in 8. Retrospective analysis showed that therapy and investigations costing £7979 could have been avoided, if CA-125 assays costing £5470 had been acted upon. The efficacy of the CA-125 algorithm is being independently verified to confirm that monthly CA-125 measurements whilst on treatment combine cost-effectiveness with a decrease in unpleasant interventions.
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INTRODUCTION

MOST PATIENTS with advanced epithelial ovarian carcinoma receive several months of aggressive chemotherapy, yet fewer than 30% remain relapse-free for more than 3 years [1–4]. Much unnecessary drug toxicity and expense could be avoided if clinicians were aware, at an early stage of treatment, which patients were clearly not benefiting from continuing the same therapy, and should be offered alternative or symptomatic therapy. Because it is so difficult to monitor the response to therapy of ovarian carcinoma, a serum tumour marker has great potential. Bast *et al.* [5] developed a monoclonal antibody OC125 that detects an antigen determined in peripheral blood, designated CA-125. This serum tumour marker is elevated in over 80% of patients with advanced epithelial ovarian carcinoma. Its level has been shown to fall in most patients whose tumour is responding to therapy and to rise in most patients whose tumour is progressing [5–12].

For a clinician to be able to act upon CA-125 levels or for a clinical trial to accept them as a measurement it is necessary to know how accurately the rise or slow fall in CA-125 levels predicts tumour progression. This requires not just looking at the slope of the curve but also that aspects of the curve be defined and then analysed. We investigated various criteria defined by CA-125 levels to produce the optimal algorithm which could define progressive disease. We then used that algorithm to determine how much ineffective chemotherapy could be avoided and what other investigations would no longer have been required.

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PATIENTS AND METHODS

Patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian adenocarcinoma were eligible for entry into this North Thames Ovary Group Trial. The intended therapy was five monthly courses of carboplatin 400 mg/m^2 followed, if no evidence of progression of disease, by a second look laparoscopy or laparotomy. Patients with less than 2 cm maximum diameter residual disease were then randomised into two arms, receiving either whole abdominal radiation or five further courses of carboplatin. Between April 1985 and October 1989, 254 eligible patients were entered into this study. 71 patients, mostly from Charing Cross Hospital and Mount Vernon Hospital had monthly serial serum samples collected. Samples were assayed in batches using a 1 step solid phase enzyme immunoassay kit (Abbott, Maidenhead, UK). The persons performing the assays had no access to clinical information on the patients. The clinicians were not aware of the CA-125 results and patients continued on planned treatment until completion of study or progression.

Progression was defined as clinical or radiological evidence of a new tumour mass or greater than 25% increase in maximum diameter of any previously measurable lesion. As CA-125 levels were only regularly measured whilst patients were having their planned therapy, we only analysed relapses that occurred during planned therapy.

RESULTS

Production of algorithm to define progression according to CA-125 levels

Until confirmation of progressive disease or completion of planned therapy, CA-125 levels were recorded and tabulated according to the criteria listed in Table 1. These criteria were selected because they were considered easy to use by clinicians, they had been used by other investigators, and they appeared to give a good prediction of progression. Any three consecutive samples during the agreed time scale were used to assess whether they fulfilled the criteria. In every case, the second sample had to fulfil those criteria and had to be confirmed by a third sample.

To be included in the algorithm for progression serum samples

Table 1. *CA-125 measurements during planned therapy*

CA-125	% of all patients	Progressed	Not progressed
<35 U/ml	69	4	45
35–≤100 U/ml	14	5	5
>100 U/ml	17	10	2
Rise >50%	9	6	0
Rise >25%–≤50%	3	2	0
<50% decrease and >100 U/ml	16	10	1
>50% rise and >35–<100 U/ml	3	2	0
<50% decrease and >35–<100 U/ml	16	8	3

No. of patients.

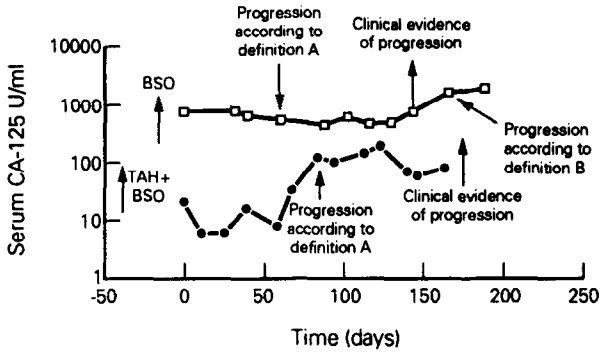

Fig. 1. Example of CA-125 values in 2 patients following bilateral salpingo-opherectomy (BSO) in 1 and total abdominal hysterectomy (TAH) + BSO in the other. Day 0 is date started chemotherapy. Definition A is 3 levels >100 U/ml, definition B is >25% rise.

had to be obtained within a set time. For absolute levels the third confirmatory sample had to be at 56 days or longer from the first sample. For a less than 50% decrease in levels the third confirmatory sample also had to be at 56 days or more from the first sample. These time limits were to reduce false positives. For rising levels the third confirmatory sample had to be at 56 days or less from the first sample. This artificial time limit was included as we wished to concentrate on the period during planned therapy.

The criteria were then analysed to find an algorithm which indicated progressive disease according to CA-125 levels. In producing an algorithm it was considered more important to err on the side of overtreating or overinvestigating false negative patients rather than stopping therapy prematurely in false positive patients, i.e. a premium was placed on specificity. The algorithms which we tested are shown in Table 2.

A rise in CA-125 levels greater than 25% gave a specificity for progression of 100% but only detected 40% of patients who progressed on therapy. To improve the sensitivity and keep the specificity as high as possible we chose a rise of greater than 25% and/or levels remaining greater than 100 U/ml with a fall of less than 50%, as the best algorithm to use in assessing potential benefits (Fig. 1). The time of progression predicted by CA-125 measurements was agreed to be 2 weeks after the date of the confirmatory CA-125 level to allow time for the assay result to be returned to the clinician. The median lead time to confirm progression from the CA-125 prediction of progression was 3 months with a range of 0–12 months (Table 3). The CA-125 predicted time of progression ranged from after the second to after the ninth course of chemotherapy (Table 3).

In analysing CA-125-predicted progression, we accepted the algorithm as true positive if there was clinical or radiological confirmation within 12 months of the time of prediction, and false positive if the interval was greater than 12 months. We accepted the algorithm as true negative if there was no confirmed progression within 4 months of the time of the CA-125 prediction and false negative if there was confirmed progression at any time whilst on therapy not predicted by CA-125.

The algorithm gave a true positive prediction in 12 patients and a false negative prediction in 8 patients, a true negative prediction in 50 patients and a false positive prediction in 1 patient. This patient's tumour was found by palpation and ultrasound scan to have had no response to chemotherapy 2 months after the CA-125 levels predicted progression. However she was considered a false positive as she has had no evidence of tumour progression over the following 30 months.

Table 2. *Progression defined by CA-125 levels*

CA-125 criteria	Sensitivity	Specificity	Positive predictive value
>100 U/ml	50	96	83
Rise >25%	40	100	100
Rise >25% & or >100 U/ml	60	96	86
<50% decrease and >100 U/ml	50	98	91
<50% decrease and >35 U/ml	70	96	88
Rise >25% & or <50% decrease and >100 U/l	60	98	92

Percentages.

Potential savings

The scans and operations to determine the disease status of the 13 patients after the CA-125 algorithm predicted progression, as well as the courses of carboplatin given after that time point, are shown in Table 3. 11 ultrasound scans, 4 computed tomographies (CT) and 1 bone scan could have been avoided if the clinician had already been convinced by the CA-125 levels

Table 3. *Time progression predicted and potential savings*

Lead time (months)	Chemotherapy course prior to prediction	Potential savings: Scans	Courses of carboplatin	Surgery
0	3	–	–	–
3	4	US	1	Laparotomy
3	3	2 US, CT	2	–
4	3	2 US	2	–
0	4	Bone scan	–	–
0	3	–	–	–
1	3	US	1	Laparotomy
3	3	–	2	–
12	3	3 US	7	Laparotomy
2	9	CT	1	–
2	2	US	3	–
5	4	CT	1	–
False positive	3	CT, US	2	–

CT = computed tomography, US = ultrasound.

that the patient had progressive disease. Similarly, three second-look laparotomies would have been cancelled. 22 courses of carboplatin were given after the patients had been shown to have progressive disease despite carboplatin, and this therapy would therefore not have been given if the clinicians had been aware of this.

The costs of each investigation including consumables and labour have been calculated as: abdominal CT £155, pelvic ultrasound scan £33, isotope bone scan £57 and each CA-125 assay £11. These costs are based upon estimates made in York [15] and Coventry (AK Szczepura, J Fletcher and JD Fitzpatrick Ref. 16). All the costs given are direct costs only; they do not contain hospital overheads or capital charge beyond the cost of the dedicated equipment. They are therefore conservative estimates, as, therefore, are the savings. The basic drug costs of carboplatin were calculated at an average of £315 per course based on a price of £78.86 per 150 mg vial including 15% VAT. The 71 patients had an average of seven CA-125 assays during their planned therapy with a total cost of £5467. The total cost of the investigations and carboplatin listed in Table 3 that could have been avoided is £7970. The potential savings by performing serial CA-125 measurements was therfore £2503 equivalent to £35 per patient.

DISCUSSION

To make clinical decisions based on CA-125 levels requires precise criteria defining progression. As there is no agreed definition, we looked at several different criteria to ascertain which could be used to give the earliest prediction of tumour progression. The algorithm which we have produced was derived and tested in the same patient group and is being validated in another set of patients. A computer program has been produced to test algorithms for both tumour progression and response to therapy. It is likely to verify the algorithm for progression as there have been several reports suggesting that serial rises in CA-125 levels can predict progression of ovarian carcinoma [5–11].

If the algorithm had been acted upon, the 1 patient with a false positive prediction would have stopped therapy two courses earlier. The fact that this lady's tumour masses had clinically failed to respond to chemotherapy, yet she still remains progression-free, fits with the observation that some women with residual ovarian carcinoma remain progression free for years off all therapy [1, 4]. This suggests that stopping or changing chemotherapy earlier because of persistently elevated CA-125 levels might not be disadvantageous.

In this study serum for CA-125 assays were only obtained monthly prior to each course of chemotherapy. To exclude laboratory error our algorithm included a confirmatory third sample. If that confirmatory sample had been requested immediately the second sample had indicated progression, and the result was available prior to the next course of chemotherapy, that course could have been avoided. Automated tumour marker follow-up systems can be programmed to generate requests for additional samples that can be sent either to the patient or her doctor [13].

With the ever increasing rise in health costs it is essential to show that new investigations are cost-effective and provide effective replacements for existing investigations. This study clearly shows that in the majority of ovarian cancer patients serial CA-125 measurements can demonstrate progression earlier than CT and ultrasound scans. Among the 40% of patients whose progression is not indicated by elevated CA-125 levels, the few with suspicious symptoms but no clinical signs of progression will still require scans. As the cost of serial CA-125 measurements is more than the scans they might replace, to be cost-effective CA-125 measurements also need to produce savings in therapy costs. We have shown that if the costs of carboplatin given after progression is included, the overall costs favour serial tumour markers. In this study the expensive drug carboplatin was used. However the cost of £315 per course of carboplatin is no more than the costs of admitting a patient for cisplatin therapy [14]. The cost of the second look laparotomies that would have been avoided has not been included as they are less frequently performed now. In addition to financial savings, serial CA-125 measurements would lead to the avoidance of unnecessary drug toxicity.

The costing of CA-125 assays has been based on a laboratory having sufficient samples to make the most efficient use of each kit. As the most favoured kits use isotopic assays of limited shelf life, laboratories with few samples to assay will incur far higher unit costs and make the use of serial CA-125 measurements of debatable financial value.

This study only investigated the savings obtained by serial tumour markers during planned chemotherapy. In patients on follow-up after chemotherapy for ovarian carcinoma a serial rise of CA-125 of >25% almost certainly indicates progression especially if confirmed by a third rising sample [7–11]. This marker rise, which precedes other manifestations of progression in over 60% of cases [11], can be used instead of scans for clinical decision-making. CA-125 assays are only cost effective compared to scans if they are performed at the first suspicion of recurrence, rather than regularly throughout follow-up. There is no evidence that early introduction of currently available treatment for relapse is of greater survival benefit than treating patients when they clinically relapse. Improvements in therapy are therefore necessary before regular markers on follow up whilst off therapy become clinically valuable. However this study does suggest that serial CA-125 assays whilst patients are on treatment are cost effective and lead to the avoidance of ineffective chemotherapy.

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Effects of Prolonged Exposure to Cisplatin on Cytotoxicity and Intracellular Drug Concentration

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The present study was designed to analyse the cytotoxic effect of cisplatin *in vitro* as a function of various exposure times (up to 120 h), keeping constant the parameter $C \times T$ (product of the drug concentration per time). Intracellular drug concentrations were measured in parallel following analysis of cisplatin influx and efflux characteristics. A head and neck cancer cell line was selected to represent the spectrum of cisplatin antitumour activity. The IC_{50} values (μg/ml) for 1, 2, 11 and 121 h were, respectively 4.51, 2.73, 0.27 and 0.151. Reduction of the IC_{50} was clearly not linearly related to prolongation of the cisplatin exposure time. The kinetics of cisplatin incorporation into CAL 27 cells was investigated as a function of different cisplatin concentrations. A plateau was reached after 16 h of contact. For the extracellular cisplatin concentrations of 1, 2.5, 5 and 10 μg/ml, the average intracellular Pt concentrations at the plateau were, respectively (ng/10^6 cells): [mean (S.D.)] 12.8 (0.98), 31.11 (5.12), 71.38 (6.03) and 136.7 (16.5). Intracellular Pt concentrations were linearly related to the extracellular drug concentration ($r = 0.99$). The drug left the cells following a two-slope kinetics pattern with an α half-life of 1.29 h and a β half-life of 94.4 h. The cytotoxic effect for a given $C \times T$ clearly differed for the different cisplatin exposure times. The longest exposure time (121 h) gave the least pronounced cytotoxicity. The intracellular Pt concentrations were linearly related to the $C \times T$ values. Cisplatin levels were much lower after the 121 h exposure. These data may prove valuable in establishing a rationale which can aid in selection of optimal modes of clinical cisplatin administration.
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INTRODUCTION

CISPLATIN IS one of the most active drugs for the treatment of cancer, and particularly testicular, ovarian, head and neck, and bladder carcinomas [1]. However, use of this drug is often accompanied by numerous and frequently severe toxicities, such as nausea and vomiting, nephrotoxicity, neurotoxicity, and ototoxicity [2]. Attempts to avoid such adverse effects include use of various analogues [3], association with neutralising agents [4], and, recently, the development of efficient antiemetics [5]. Another approach is based on modification of the duration of cisplatin infusion. Alternatives to short administration durations, such as continuous 5-day infusions, dramatically reduce acute nausea and vomiting without loss of efficacy [6]. A pharmacological rationale serving as a guideline for selection of optimal cisplatin administration schedules would be helpful. Such information can be obtained from both pharmacokinetic explorations and experimental studies. The pharmacokinetic investigations conducted so far on various cisplatin infusion durations represent a good basis of knowledge [7–13]. By

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