Annals of Oncology 7: 361–364, 1996.

Original article

Defining progression of ovarian carcinoma during follow-up according to CA 125: A North Thames Ovary Group study

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Summary

Background: Many studies have shown that CA 125 levels frequently rise prior to clinical evidence of progression of ovarian cancer. For clinical trials an accepted definition of progression according to CA 125 is required. We therefore determined what change in CA 125 level was the most accurate predictor of relapse in patients on follow up after therapy for ovarian cancer.

Patients and methods: Serial CA 125 levels were studied from 255 patients entering the North Thames Ovary Trial of 5 *versus* 8 courses of chemotherapy. An initial analysis was made 2 months after closure of the trial, a more detailed analysis was made after 81 confirmed relapses among evaluable patients and a final analysis was made one year later with longer follow-up.

Results: On the basis of the results from the interim analyses and the cut-off level of 22–35 U/ml used by different laboratories, 30 U/ml was chosen as the upper limit of normal. In the final analysis a doubling of CA 125 from the upper limit of normal was defined as progression. Using this method sensitivity was 85.9%, specificity 91.3%, positive predictive value 94.8%, and negative predictive value was 77.8%. Insisting on a confirmatory elevated CA 125 level reduced the false positive rate to <2% with a sensitivity of 83.9%. The median lead-time prior to clinical progression was 63 days.

Conclusion: A confirmed rise of serum CA 125 level to more than twice the upper limit of normal during follow up after first line chemotherapy accurately predicts tumour relapse.

Key words: CA 125, ovarian cancer, progression, relapse, tumour marker

Introduction

The efficacy of chemotherapy in ovarian cancer patients is routinely evaluated by physical examination and imaging techniques. However, these methods are unreliable for monitoring, as progressive and recurrent disease often remains hidden until the patient presents with a large tumour mass. Fortunately, more than 85% of ovarian cancer patients have CA 125 levels above 35 U/ml [1, 2] and the marker seems to give reliable information about disease status. A rise of CA 125 of 50% [3], 100% [1], or to just above the cut-off level [4] has been shown to predict progression of ovarian cancer, there is no agreed definition for progression. For use in clinical trials it is essential to have a precise definition for progression and to know how accurate it is. We therefore tested various changes in CA 125 level to determine which was the most accurate predictor of progression in a large group of patients.

Patients and methods

The analyses were performed on blood samples from patients with FIGO stage IC–IV entering the North Thames Ovary Trial of 5 *versus* 8 courses of carboplatin or cisplatin. The study was carried out over a 5-year period from 5.12.89 to 13.4.94. The data were collected retrospectively, using all available CA 125 values. Time between samples varied from <1 month to >6 months. It was noted that in some patients CA 125 levels could continue to rise for many months before progressive disease became detectable clinically, and it was therefore decided to allow a follow-up of 12 months before a prediction of progression by CA 125 would be termed a false positive prediction of progression. CA 125 was measured initially by the CIS immunoradiometric assay but since 3.8.92 by the Cobas core ELISA assay (Roche).

Results

Three separate analyses of the CA 125 results were made over a period of 18 months.

First interim analysis

The first 237 patients had been enrolled into the trial by 3.12.93 and the first interim analysis was made 6 months later in June 1994. Thirty-four patients had to be excluded from the marker analysis because they had very few CA 125 samples (<4) or had been given monoclonal antibody treatment which causes falsely elevated levels of CA 125. The remaining 203 eligible patients were divided into 3 groups:

Group 1 – patients whose CA 125 values always remained in the normal range using 40 U/ml as an upper normal level (21 patients (10.35%));

Group 2 – patients whose CA 125 values both rose and fell above and below the normal level (124 patients (61.08%));

Group 3 – patients whose CA 125 values were persistently above normal (58 patients (28.57%)).

Group 1 patients never had elevated levels of CA 125 even at clinical progression. Group 3 patients had persistently elevated levels of the marker suggesting either progression of disease or residual disease despite first line chemotherapy. We have previously proposed precise definitions for progression according to CA 125 values during therapy which are applicable to these patients [5]. Initial analysis was therefore performed only on group 2 looking for the date of the first value rising from ≤40 U/ml to ≥60 U/ml, and from ≤40 U/ml to ≥100 U/ml. The results of this analysis are shown in Table 1.

Second interim analysis

At the time of the initial analysis several patients had rising CA 125 values which predicted progression but had no signs of clinical progression (Table 1). When all these apparently false positive predictions had been followed for greater than 12 months, the analysis was performed again. The analysis was then extended using variations of the CA 125 rise ≥50% of a normal cut-off level or a doubling of a normal cut-off level, looking at rises from ≤22 U/ml to ≥33 U/ml, ≤20 U/ml to ≥40 U/ml, ≤30 U/ml to ≥45 U/ml, ≤30 U/ml to ≥60 U/ml, and ≤40 U/ml to ≥60 U/ml (Table 2). The levels of 22 U/ml, and 30 U/ml, were chosen as several laboratories have selected those levels as their upper limits of normal, whilst 20 U/ml and 40 U/ml were chosen to fit in with our previous definitions [5]. The total number of 145 patients from groups 1 and 2 was included in this analysis to give a more realistic assessment of sensitivity. The prediction of progressive disease by CA 125 was prior to the date of clinical progression in 79%–83% of the cases depending on the used prediction.

Table 1. The ability of serum CA 125 to predict early progression in 124 patients by using only one rising value from ≤40 U/ml to ≥60 U/ml, and from ≤40 U/ml to ≥100 U/ml.

	1 value ≥60 U/ml	1 value ≥100 U/ml
True positive (TP)	58 (+5[a]) = 73	60 (+4[a]) = 64
False positive (FP)	7 (−5[a]) = 2	4 (−4[a]) = 0
True negative (TN)	44	46
False negative (FN)	5	14
Sensitivity (SE)	93.2%–93.6%	81.1%–82.1%
Specificity (SP)	86.3%–95.7%)	92.0%–100%
Positive predictive value (PPV)	90.7%–97.3%)	93.8%–100%
Negative predictive value (NPV)	89.8%	76.7%
Median lead-time[b] (range)	−63 days (−350 to +77)	−31.5 days (−245 to +105)

[a] Number of patients with follow-up <1 year and no signs of clinical progression.

The range of sensitivity, specificity and positive predictive value has been calculated including or excluding the patients with <1 year follow-up.

[b] – numbers are days that CA125 predicted progression before clinical progression; + numbers are days that clinical progression preceded CA 125 predicted progression.

Table 2. The ability of serum CA 125 to predict early progression by using 50% rise, or a doubling of the normal CA 125 cut-off level.

	Rise from <22 to >33	Rise from <20 to >40	Rise from <30 to >45	Rise from <30 to >60	Rise from <40 to >60
Total patients	119 (9[a])	115 (8[a])	135 (13[a])	135 (13[a])	145 (21[a])
TP	53	52	65	66	73
FP	10	6	6	4	4
TN	52	53	57	57	60
FN	4	4	7	8	8
SE	93.0%	92.9%	90.3%	89.2%	90.1%
SP	83.9%	89.8%	90.5%	93.4%	93.8%
PPV	84.1%	89.7%	91.5%	94.3%	94.8%
NPV	92.8%	93.0%	89.0%	87.7%	88.2%
Median lead-time (range)	−86 days (−357 to +216)	−74 days (−361 to +216)	−75 days (−361 to +216)	−67 days (−361 to +77)	−66 days (−361 to +77)

[a] Number of patients included in the analysis with all CA 125 values <22 U/ml, <20 U/ml, <30 U/ml, <30 U/ml, and <40 U/ml in the above 5 groups, respectively.

Final analysis

On the basis of the results from the interim analyses and the cut-off level of 23–35 U/ml used by different laboratories, 30 U/ml was chosen as the upper limit of normal and a doubling of the normal cut-off level as a definition of progression in the final analysis made in December 1995. A total number of 255 patients entered the North Thames Ovary Trial, 18 more than when the first analysis was performed. After the review of the hospital records 20 patients were found to be ineligible for the final analysis due to secondary malignancy in 7 patients and treatment with monoclonal antibody in 13 patients. An additional 104 patients were considered CA 125 not evaluable. Twelve of the 104 patients had less than 3 CA 125 samples, 88 patients had all samples greater than 30 U/ml, in 3 patients the last sample was taken 3–6 months prior to clinical progression, and the remaining one patient with a prediction of progressive disease by CA 125 had follow-up of less than 12 months. Thus, 131 of 255 patients were considered evaluable for evaluation of CA 125 values.

The results of the analysis looking at a rise from ≤30 U/ml to ≥60 U/ml are shown in Table 3. Fourteen patients with all CA 125 levels ≤30 U/ml were includ-

Table 3. The ability of serum CA 125 to predict early progression in 131 patients by using a doubling of the normal cut-off level (30 U/ml).

	Rise from ⩽30 U/ml to ⩾60 U/ml
TP	73
FP	4
TN	42
FN	12
SE	85.9%
SP	91.3%
PPV	94.8%
NPV	77.8%
Median lead-time (range)	−63 days (−361 to +77 days)

Table 4. The ability of serum CA 125 to predict early progression by using 2 consecutive values greater than a doubling of the normal cut-off level.

	2 consecutive values ⩾60 U/ml
Number of patients	130 (119[a])
TP	73 (62[a])
FP	1
TN	42
FN	14
SE	83.9% (81.6%[a])
SP	97.7%
PPV	98.6% (98.4%[a])
NPV	75.%
Median lead-time (range)	−63 (−80.5[a]) days (−361 to +77)

[a] Figures after excluding the patients with a confirmatory sample taken during second-line treatment (2 patients) and patients without a confirmatory sample (9 patients).

ed in the analysis but only 4 of them had a false negative prediction of progression by CA 125. Furthermore, all 6 patients with Borderline tumour and one patient with mixed Mullerian tumour had a true negative prediction. It must be also emphasized that in 3 of 4 patients with false positive results CA 125 predicted progressive disease prior to clinical detection by 371, 529, and 597 days, respectively, which would be probably termed as true positive by other authors. The fourth false positive patient started second-line chemotherapy on the basis of rising CA 125 values prior to clinical confirmation of progression.

CA 125 values became elevated ⩾60 U/ml before clinical progression in 55 (75.4%) of 73 true positive patients with a median lead-time of 94 days (range 2–361). In an additional 9 patients (12.3%) the date of progression predicted by CA 125 coincided exactly with the date of clinical progression. Clinical progression preceded the marker changes in the remaining 9 patients (12.3%) with lead-times of 1, 1, 2, 3, 5, 12, 36, 46, and 77 days, respectively. In these 9 patients CA 125 was not measured at the time of clinical detection of progressive disease. It seems, however, unlikely that CA 125 could have predicted progression in these patients in order to start early second-line treatment, as the median time from last sample to clinical progression was only 2 months.

The analysis was then extended using 2 increased CA 125 values, the second one for a confirmation of progression (Table 4), as the false positive results could be due to just one single abnormal CA 125 level. Using this method, 2 of 4 false positive patients never had another rise in CA 125 levels and one patient became non-evaluable owing to follow-up shorter than 12 months. Among true positives, 9 patients had no confirmatory sample measured although follow-up was continued and 2 patients had a confirmatory sample taken during second-line treatment. The figures in Table 4 were calculated after both including and excluding these 11 patients. In other patients the second CA 125 value confirmed the previous results.

Discussion

There is no consensus regarding the routine use of CA 125 for follow-up of ovarian cancer [6]. This is because of uncertainty as to the accuracy of CA 125 in predicting relapse and lack of evidence as to the benefits of treating relapsing disease early. This study has clearly shown that a simple definition based on doubling of CA 125 levels from the upper limit of normal, accurately predicts progression of ovarian carcinoma in patients on follow-up. When the doubling was confirmed by a second sample there was only one false positive prediction of progression among 86 patients with clinically or scan proven progression. It is possible that the one false positive patient had disease that was still subclinical. Because she received second line therapy based just on rising CA 125 levels and still has no clinical evidence of progression it will remain unclear whether her most recent therapy was unnecessary.

The number of patients whose CA 125 levels have falsely predicted progression can be reduced by insisting on doubling of CA 125 levels and a confirmatory sample. Bast et al. [1] saw no false positives among 17 patients whose CA 125 levels doubled. Van der Burg [4] analyzed 98 patients and from 449 samples found 7 CA 125 values that increased between 36–45 U/ml without apparent progression. A larger rise would have avoided these false positives. A cut-off of 15 U/ml was proposed by Gard and Houghton [7] with the suggestion that chemotherapy should be commenced if a repeat sample was >35 U/ml. In our analysis of patients with a rise of CA 125 levels from ⩽22 to ⩾33 U/ml there were 10 false positives which reduced to 6 false positives when a rise from ⩽20 to ⩾40 U/ml was required, to 4 when a rise of ⩽30 to ⩾60 U/ml was required and to just one when a confirmatory sample was required. Despite making the requirements stricter the final definition still detected progression in 84% of

cases. Lowering the threshold for progression according to CA 125 would improve the lead-time at the expense of increasing the false positives.

Our proposed definition for progression is only valid during follow-up after initial therapy for ovarian carcinoma. To predict progression during therapy when CA 125 levels are already elevated requires more complicated definitions [5]. Providing other conditions which could lead to a rise in CA 125 levels, such as non malignant inflammatory disease, cirrhosis, endometriosis and surgery have been be excluded, there is less than 2% chance of falsely predicting tumour progression.

A major dilemma is what to do about a rising CA 125 level. The options include continued follow-up until symptoms or signs of relapse, investigating then retreating if relapse is confirmed and immediate treatment. The MRC gynaecological cancer working party and the EORTC gynaecological cancer cooperative group have recently started a randomised trial which should determine whether there is any benefit from early chemotherapy based on our CA 125 definition compared to delaying chemotherapy until relapse is detected clinically. Until the results of that trial are available, performing CA 125 levels routinely during follow-up will continue to cause more anxiety and confusion than proven clinical benefit. However, this study demonstrates that if CA 125 is measured when there is clinical suspicion of relapse and has risen from the normal range at the end of chemotherapy to twice the upper limit of normal, there is a greater than 94% probability of tumour relapse. The probability of relapse rises to greater than 98% if the rise is confirmed by a second sample. This predictive power suggests that confirmatory scans are unnecessary. We therefore recommend that serum CA 125 should be measured at the end of chemotherapy and whenever relapse is suspected but that regular CA 125 measuremenets during follow-up should only be performed as part of a clinical trial.

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Received 25 January 1996; accepted 27 March 1996.

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