DETERMINATION OF CANCER ANTIGEN 125 IN OVARIAN CARCINOMA

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ABSTRACT

Appropriate therapeutic measures can improve the life expectancy of patients with ovarian malignancy. There has been a pressing need for serodiagnostic assays to enable the close patient monitoring. Cancer Antigen 125 (CA125) has been described as a useful marker in patient monitoring for ovarian malignancy. Keeping this in view, the present study was planned. 40 consecutive female patients of ovarian carcinoma (mean age 52.4 ± 10.7 years) were selected for serum CA125 analysis during the period of year 1995-2001. The tumour marker concentration was compared with histologic types of ovarian tumour and the FIGO staging of the disease. 25 healthy females (mean age 35.2 ± 10.4 years) served as control. Mean serum CA125 concentrations in patients with papillary serous adenocarcinoma (Mean $\pm$ % CV 1571 ± 121.5 U/ml) was much higher than patients with mucinous adenocarcinoma (775 ± 78 U/ml). Mean serum CA125 concentration in endometrioid carcinoma was very high (2853 ± 136 U/ml). The patient with clear cell carcinoma however had shown moderate increase (60 U/ml). No correlation was found between serum CA125 concentration and the FIGO staging of disease.

Quantitation of CA125 was most helpful in monitoring the response of treatment and followup of the patients after completion of their treatment. Posttherapeutically its concentration showed more than 50 % reduction in almost all (91.4%) patients ($P < 0.001$). Importantly these patients had also shown significant regression of the disease clinically and radiologically. 8.6 % of patients had shown static or increase in serum CA125 concentration which was associated with either clinically static or progressive disease. Recurrence of the disease was noted in patients who had shown increase in serum CA125 concentration (biochemical recurrence) in the followup

However, in our test population biochemical recurrence (increase in serum marker concentration) preceded the clinical or radiological recurrence by an average of 6.5 months.

Kaplan meier survival analysis for evaluation of overall survival in our test subjects showed an overall survival of 32% at one year and median survival of 9 months with confidence interval of 6.34 to 11.66. We conclude that serum CA125 is a useful marker for monitoring the treatment and predicting an early recurrence of the disease in ovarian carcinoma patients. A study in larger number of patients is needed to define its exact role in the management of the carcinoma ovary.

KEY WORDS

Serum CA125, Epithelial tumour, Ovarian Carcinoma.

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INTRODUCTION

The patients of ovarian cancer cannot be adequately monitored by computed tomography (CT Scan) or ultrasound (U/S) scans only(1). There is a need for certain serum markers which are good prognostic predictors and are easy to assay. Serum CA125 is one such marker which is commonly used in diagnosis as well as management of epithelial tumors of ovary. Preoperative CA125 levels(2,3), postoperative levels(4), absolute levels after chemotherapy(5) and rate of fall(6) after the first cycle of chemotherapy have all been advocated as useful prognostic indicators in epithelial ovarian cancer. Prognostic significance of early CA125 assay has also been reported in epithelial ovarian carcinoma(7). However, according to Welandar 1992 (8) & Kenemans et al. 1994(9), CA125 in the immediate postoperative period was not a significant predictor of either progression free or overall survival.

This retrospective study was planned to find the utility of serum CA125 assay in diagnosis and monitoring the treatment of epithelial ovarian malignancy and whether it has any correlation with staging and histologic types of ovarian carcinoma.

MATERIALS AND METHODS

Serum samples were obtained from 40 female patients (mean age 52.4 ± 10.7 years) with clinically and histologically verified epithelial ovarian cancer over a period of 7 years from 1995-2001. Out of these, 33 patients had papillary serous adenocarcinoma (82.5%), 4 had mucinous adenocarcinoma (10.0%), 2 had endometrioid carcinoma (5.0%) and only one patient was reported to have clear cell carcinoma (2.5%)(Table I). Tumor staging was done according to FIGO classification. As shown in table II, out of 40 patients 8 had stage I disease (20.0%), 4 had stage II (10.0%), 17 had stage III (42.5%) and 11 were with stage IV disease (27.5%)

25 healthy females (Mean age 35.2 ± 10.4 years) served as control. Serum CA125 was determined by streptavidin biotin EIA (M/s Roche diagnostics). The antibodies against serum CA125 were M11 & OC125 (Centocor, melfern, Pa.) which were highly specific for this molecule. The upper reference limit was taken as 35 U/ml for non-pregnant healthy females.

Treatment Protocol

All patients were treated with debulking surgery followed by 6 cycles of chemotherapy comprising Cis platinum and Cyclophosphamide or Cis platinum and Paclitaxal.

Statistical Analysis

No statistical analysis could be performed to calculate the statistical significance between CA125 concentrations and various histologic types of tumor, due to unequal distribution of patients within each group. Kruskal wallis oneway nonparametric anova test was applied to calculate the p value to compare serum CA125 concentrations within various clinical stages of disease.

To assess the response of therapy, Wilcoxon Signed Ranks Test was performed to calculate the p value between pre therapeutic and post therapeutic serum CA125 concentrations.

Serial determination of serum CA125 was done after each chemotherapy cycle and then 2 monthly during followup period in all the patients to calculate the mean biochemical recurrence time. The overall survival in ovarian carcinoma patients was calculated by Kaplan meier survival analysis.

RESULTS

All results are expressed as mean $\pm$ % CV. Mean serum CA125 concentration in papillary serous adenocarcinoma patients ($n = 33$) was 1571 ± 121.5 U/ml whereas in mucinous adenocarcinoma ($n = 4$) it was much less (Mean $\pm$ % CV 775 ± 78 U/ml). One patient out of 33 papillary serous adenocarcinoma patients had shown marginal increase in serum CA125 concentration (38 U/ml). This patient had stage IIIC disease clinically and radiologically. The patients of endometrioid carcinoma had very high serum CA125 levels i.e. 2853 ± 136 U/ml. The only patient of clear cell carcinoma had shown moderate increase in serum CA125 concentration (60 U/ml). Due to unequal distribution of patient number within each group, no statistical analysis could be performed to compare the tumor marker levels in relation to tumor type, hence definite conclusion could not be drawn on histological types of tumor and serum CA125 levels due to small number of patients in latter three groups (Table I)

Staging of the disease was done on the basis of FIGO classification. No correlation was found in serum CA125 concentration and FIGO staging of the disease. Patients in stage I had significantly

higher concentrations of serum CA125 than patients with stage II, III and IV ($P < 0.001$). The difference in serum CA125 concentrations was nonsignificant ($p < 0.9$) among the patients with stages II, III and IV disease (Table 2).

Determination of serum CA125 concentration was most useful in monitoring the response of therapy. All these patients of ovarian carcinoma had very high pretherapeutic serum CA125 concentrations. In 91.4% of these patients, posttherapeutic reduction in CA125 levels was more than 50%. Wilcoxon Signed Rank Test suggested highly significant reduction in serum marker levels ($p < 0.001$). Importantly, these patients also showed clinical & radiological regression of the disease. 8.6% of the patients showed static or increased serum CA125 concentration after therapy which was associated with either static disease or tumor progression.

Serial determination of serum CA125 during the course of treatment and followup was extremely helpful in detection of early recurrence. In our test population, biochemical recurrence preceded clinical or radiological recurrence by mean value of 6.5 months (mean $\pm$ SD 6.57 ± 2.8 months).

Fig1 shows serum CA125 profile in a patient with papillary serous adenocarcinoma (stage III). Her serum CA125 concentration was very high (> 2000 U/ml) before treatment. Regression in disease was also noted radiologically after chemotherapy with normalization of serum CA125 concentration. Increasing trend in serum CA125 was detected, 9 months (Area marked with arrows) before clinical recurrence could be picked up in CT scan.

Kaplan meier survival analysis to evaluate overall survival in these patients had shown an overall 1 year survival of 32 % and a median survival time of 9 months with 95% confidence interval (CI) of 6.34 to 11.66 (Fig.2).

DISCUSSION

CA 125 is an antigenic determinant on a 2,00,000 D mucin like glycoprotein epitope, recognized by a monoclonal antibody OC125 (10). The epithelial surface of the normal ovary is not positive for CA125 staining but cells lining ovarian cysts as well as papillary excrescences within ovarian cysts are often positive (11). In our test population, almost all patients had very high serum CA125 at the time of diagnosis except one patient of papillary serous

adenocarcinoma stage IIIC, who had shown marginal rise in her serum CA125 (38 U/ml). In all other patients of papillary serous adenocarcinoma, serum CA125 concentrations was much higher as compared to mucinous adenocarcinoma patients. Kudoh et al 1999 (12) have reported similar findings in a comparative study of tumor markers in patients with primary epithelial ovarian carcinoma. In their patient population, serum CA125 in papillary serous adenocarcinoma patients, was significantly higher than mucinous adenocarcinoma patients. These mucinous adenocarcinoma patients were mostly in stage I, which was suggestive of slow growth and less invasive character of this tumor. The patients with endometrioid carcinoma had much higher CA125 concentration as compared to other types of tumors although the sample size of endometrioid carcinoma in our test population was very small. The patient with clear cell carcinoma had moderate rise in her serum marker levels.

In our test series, no correlation was found between serum CA125 concentration and FIGO staging of the disease. This suggests that CA125 may not have any correlation with tumor staging. Mayo medical lab communique 1987 (13) reports have shown no correlation of serum CA125 with tumor burden, similarly Munstedt et al 1997 (11) have not found any correlation of high FIGO staging & presence of ascitis with serum CA125 concentration. On the contrary, Kudoh et al 1999 (12) have shown increase in serum CA125 with increase in staging of the disease.

The utility of serum CA125 monitoring in ovarian carcinoma patients was extremely helpful in defining the response to therapy and detecting an early recurrence of the disease. In our test series, 91.4% of the patient had more than 50% reduction in their serum CA125 after surgery and chemotherapy ($P < 0.001$). Interestingly, these patients had also shown clinical and radiological regression of disease. Rest of the patients (8.6%) had less than 50% reduction in their serum CA125 concentration. Clinically no significant regression was noted in these patients. According to Bast et al 1983 (14) decreasing concentration of serum CA125 after therapy was associated with good response to therapy. Increasing or static serum CA125 concentration was associated with either tumor progression or static disease. In another study, Keneman et al 1994 (9) have suggested similar changes in serum CA125 concentrations which

matched well with tumor mass progression and regression. According to Rustin et al 1992 (1), serial CA125 measurements during and after therapy predict progression of disease more accurately and can be used to alter patient management. However there is no general consensus on the extent of fall of CA125 concentrations after therapy. Vander Burg et al 1993 (15) have shown a significant decrease, generally halving of the serum CA125 posttherapeutically and was shown to correlate well with clinical response in 87% of 237 patients from their 12 studies.

In our test population, recurrence of the disease was noted by rise in serum CA125 concentration by mean value of 6.5 months earlier than any clinical or radiological investigation. Therefore we suggest that patients with ovarian carcinoma should get serial estimation of serum CA125 done during the course of their treatment. Rising trend in serum CA125 will indicate appearance of early recurrence.

Kaplan Meier survival analysis in our patient population had shown overall 1 year survival of 32% and median survival of 9 months with 95% CI of

6.34 to 11.66 in our patients. Kudelka et al 1996 (16) have reported the median survival of 10 months in their patients.

CONCLUSION

Serum CA125 concentration was much higher in papillary serous adenocarcinoma of ovary. No correlation was found between serum CA125 with staging of disease. Utility of its determination is more in monitoring response to chemotherapy.

Early detection of recurrence is possible at least 6.5 months prior to any clinical or radiological recurrence if serial determination of serum CA125 is done during the course of the treatment.

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Table I

NUMBER OF PATIENTS AND THEIR SERUM CA125 LEVELS
(MEAN $\pm$ % CV) ACCORDING TO HISTOLOGICAL TYPES OF OVARIAN CARCINOMA.

	HISTOLOGICAL TYPES OF OVARIAN CARCINOMA				
	TOTAL	PAPILLARY SEROUS	MUCINOUS	ENDOMETROID	CLEAR CELL
NO.	40	33	4	2	1
Percent		82.5	10.0	5.0	2.5
SERUM CA125 (U/ml)		1571 $\pm$ 121.5	775 $\pm$ 78	2853 $\pm$ 136	60

Table 2

NUMBER OF PATIENTS AND THEIR SERUM CA125 LEVELS (MEAN $\pm$ % CV) ACCORDING TO
HISTOLOGICAL STAGING OF DISEASE

	HISTOLOGICAL FIGO STAGING				
	TOTAL	I	II	III	IV
NUMBER	40	8	4	17	11
PERCENT		20.0	10.0	42.5	27.5
S. CA125(U/ml)		4192 $\pm$ 84.5 *	1184 $\pm$ 128	1273 $\pm$ 112.4	1251 $\pm$ 89.3**

p VALUE * < 0.001 **<0.9

Fig 1 : Followup profile of serum CA125 of a patient with papillary serous adenocarcinoma. Note the early rise in CA125 (area marked with arrow) well before radiological recurrence.

FIG 1

Fig 2 : Kaplan Meler curve between cumulative survival and followup (in months) of patients to calculate overall survival in ovarian carcinoma patients.

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