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Original Research Article

Role of CA 125 in predicting pathological response and recurrence in advanced stage non mucinous epithelial ovarian cancer

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ABSTRACT

Background: Ovarian cancer is the most common gynaecological malignancy. Neo adjuvant chemotherapy (NAC) followed by interval cytoreduction is proven to be non-inferior to primary debulking surgery in advanced stage epithelial ovarian cancers (EOC). The data about patterns of reduction of CA125, its cut off value to predict chemotherapy response and recurrence in patients who receive NAC is heterogeneous with varying cut offs. This study aims to evaluate the role of CA125 as a predictive marker of pathological response and recurrence in cases of advanced EOC and to determine cut off for the same.
Methods: This is a prospective study conducted in department of medical oncology, from December 2019 to May 2021. Patients of advanced stage EOC who are on NAC with carboplatin and paclitaxel combination were included (n=33). CA125 values before treatment, after each cycle of chemotherapy, post-surgery, during the course of adjuvant chemotherapy and every 2 months post treatment were noted. As the patient undergoes interval cytoreduction, histopathology reports were followed for chemotherapy response score (CRS). Imaging was done to detect recurrence during follow up, if CA 125 value increases.
Results: The level of CA125 after third cycle of NAC showed significant correlation with chemotherapy response score and DFS in all the patients who were operable at the end of NAC. Patients with normal CA125 value (i.e. <35 U/ml) post 3 cycles chemotherapy had increased chance of having CRS 3 and longer DFS in patients with high grade serous carcinoma. Decline in CA125 value to less than 10 IU/ml post interval cytoreduction also correlates with DFS.
Conclusions: Our study shows that CA125 levels before cytoreductive surgery predicts CRS and DFS of women undergoing NAC for advanced stage EOC.

Keywords: CA125, Chemotherapy response score, DFS, Epithelial ovarian cancer, NAC

INTRODUCTION

Ovarian cancer has the highest mortality rate of the three main malignant tumours of the female reproductive system, with a 5-year OS of only 20-30%.[1] The most widely used marker of ovarian cancer, often considered the 'gold standard' is CA125.[2] However, controversy exists regarding the ability of the tumour marker to predict optimal debulking and moreover of the proper cut-off limit to do so.[3] Several studies have shown interest in using the CA125 value to predict optimal debulking, to evaluate platinum sensitivity and to monitor the disease after treatment in advanced stage ovarian cancer (FIGO stage III, IV, bulky disease).[4] For patients receiving primary cytoreduction, a preoperative CA125 level of 500 UI/ml was used as the proper cut-off limit for this purpose.[5] For patients receiving Neo adjuvant chemotherapy (NAC), different cut-offs were published, ranging from 20 to 100 UI/ml.[6] The prognostic significance of preoperative and postoperative CA125 levels has been established. Serum levels of CA125 generally reflect volume of disease. In addition, high CA125 levels may predict unresectability and an inferior survival. Postoperative CA125 levels appear to have greater prognostic significance.[7] Early diagnosis of recurrences of Epithelial ovarian cancer (EOC) has great significance for its treatment and

prognosis.[8] The chemotherapy response score (CRS) assesses histological effect in ovarian cancer after neoadjuvant chemotherapy (NAC). The CRS is associated with progression-free and overall survival.[9] Chemotherapy response score (CRS) score is summarized as follows-score 1: no or minimal tumour response (mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci); score 2: partial tumor response (multifocal or diffuse regression associated fibro-inflammatory changes, with viable tumor ranging from diffuse sheets, streaks or nodules, to extensive regression with multifocal but easily identifiable residual tumour; score 3: complete or near-complete response (mainly regression, with few irregularly scattered individual tumour cells or cell groups, all measuring <2 mm.[10] In the publication by Bohm and colleagues that described and validated the CRS, histological regression in the primary adnexal tumour did not stratify patients into prognostic groups and adnexal response scores showed inferior reproducibility; in contrast, omental scores were prognostic and reproducible.[10]

METHODS

This was a prospective study conducted in department of medical oncology from December 2019 to May 2021.

Cases of newly diagnosed epithelial ovarian cancer requiring neo adjuvant chemotherapy with paclitaxel and carboplatin combination were included in the study.

Peripheral blood 2 ml was collected and CA125 level was determined using chemiluminescence assay, performed according to the manufacturer's specifications; the normal value range is ≤35 U/ml. CA125 values before treatment, after each cycle of chemotherapy, post-surgery was noted. After that it is done once in 2 months unless progression is present. At the end of three cycles of NAC, operability was assessed. As the patients undergo interval cytoreduction, histopathology reports were followed up and chemotherapy response score was noted. After completing adjuvant chemotherapy patients were monitored with CA125 levels.

During the period of follow up if the CA125 rises beyond normal CT abdomen and chest x ray had to be done irrespective of the patient being symptomatic or asymptomatic. They were to be diagnosed to have recurrence based on CT abdomen. In a symptomatic patient PET CT was done if CT abdomen was negative for recurrence. Socio demographic variables and study variables were analysed as proportions or percentages for categorical variables and mean±SD were analysed for numerical variables. ROC curve was used to find out the cut off value of CA 125 for predicting recurrence of disease. Spearman's correlation coefficient was applied for obtaining the relationship of log difference of CA125 value with CRS score and DFS. Chi square test was used to know role of CA125 in predicting pathological response and DFS.

RESULTS

In our study out of 33 patients, 3 (9.1%) patients in the age group of 30-35, 3 (9.1%) patients in the age group of 36-40, 4 (12.1%) patients in the age group of 41-45, 7 (21.2%) patients in the age group of 46-50, 4 (12.1%) patients in the age group of 51-55, 2 (6.1%) patients in the age group of 56-60, 8 (24.2%) patients in the age group of 61-65 and 2 (6.1%) patients in the age group of 71-75 (Figure 1). Out of 33 patients, 31 (93.9%) patients were FIGO stage III and 2 (6.1%) patients were FIGO stage IV.

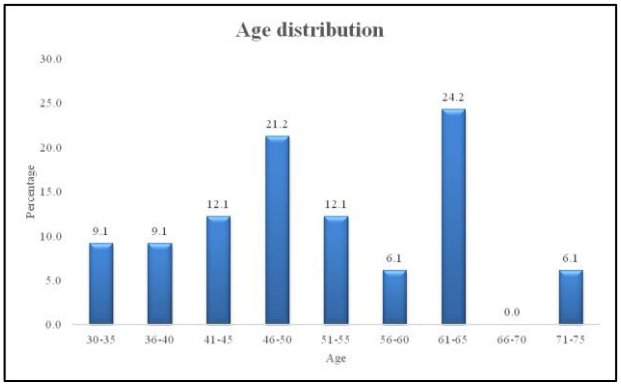

Figure 1: Age distribution.

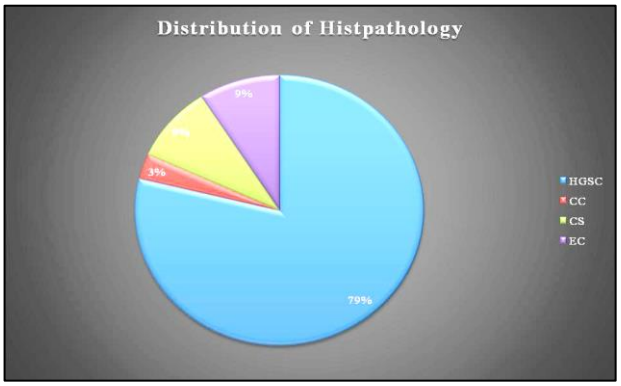

Figure 2: Distribution of Histopathology subtypes among study population (n=33).

Out of 33 patients, 26 (78.8%) patients had high grade serous carcinoma (HGSC), 1 (3.0%) patient had clear cell carcinoma (CC), 3 (9.1%) had carcino sarcoma (CS) and endometrioid carcinoma (EC) (Figure 2).

Table 1: Distribution of CRS score of study population (n=27).

CRS score	Frequency	Percentage
I	2	7.4
II	20	74.1
III	5	18.5
Total	27	100.0

27 patients out of total 33 subjects were operable at the end of 3 cycles of neo adjuvant chemotherapy (81%). Out of 27 patients, 2 (7.4%) patients had CRS score 1, 20 (74.1%) patients had CRS score II and 5 (18.5%) patients had CRS score III (Table 1).

Table 2: Distribution of disease status of study population at the end of the study (n=27).

Disease status	Frequency	Percentage
Patients who relapsed at the end of the study	13	48.1
Patients who are disease free at the end of the study	14	51.9
Total	27	100.0

Table 3: Correlation of log difference of CA125 value from baseline to third chemo with CRS score and DFS (n=27).

Variables	CA 125 (U/ml) log difference		
	N	Pearson correlation	P value
CRS score	27	-0.261	0.189
Disease free survival	27	-0.216	0.279

14 (51.9%) patients were disease free at the end of the study and 13 (48.1%) patients had relapsed at the end of the study. Patients who were operated after neo adjuvant chemotherapy were considered for analysis (n=27) (Table 2).

Correlation of log difference of CA125 value from baseline to third cycle chemotherapy with CRS score and DFS was not significant (Table 3).

Table 4: Correlation of log CA125 value after third chemo with CRS score and DFS (n=27).

Variables	CA125 after third chemo (U/ml)		
	N	Correlation coefficient	P value
CRS score	27	-0.536	0.004
DFS	27	-0.397	0.040

CA125 value after third chemotherapy had significant positive correlation with CRS score and DFS (Table 4). Normal CA125 values after third cycle of chemotherapy has significant correlation with DFS (disease free survival) (Table 5).

Post cytoreduction CA125 values have significant correlation with disease free survival (Table 6). Patients who have CA125 level ≤10 u/ml post interval cytoreduction have likelihood of longer disease-free survival compared to those with CA125 >10 u/ml.

In patients with high grade serous carcinoma (HGSC), CA 125 value after third cycle of chemotherapy has significant correlation with DFS (Table 7). Normalisation of CA125 level has correlation with both CRS and DFS among patients with HGSC (Tables 8 and 9).

Table 5: Correlation of normal CA125 value after third chemo with DFS (n=27).

CA 125valueafter 3 cycles neoadjuvant chemotherapy (U/ml)	DFS (in months)				Chi square value	P value
	>12 months		<12 months			
	n	%	n	%		
≤ 35.0	9	64	5	6	9.258	0.002
>35.0	1	8	12	92		

Table 6: Cut off value of post cytoreduction CA125 with DFS (n=27).

Postinterval cytoreduction CA 125 (U/ml)	DFS (in months)				Chi square value	P value
	>12 months		<12 months			
	n	%	n	%		
≤10	9	69	4	31	11.143	0.001
>10	1	7	13	93		

Table 7: Correlation of log CA125 value after third chemo with CRS and DFS in high grade serous carcinoma (HGSC) subgroup (n=24).

Variables	CA125 after third cycle neoadjuvant chemotherapy		
	N	Correlation coefficient	P value
CRS	24	0.185	0.3
DFS	24	0.689	0.01

Table 8: Correlation of normal CA125 value after third chemotherapy with CRS in patients with HGSC (n=24).

CA125 value after 3 cycles neoadjuvant chemotherapy (U/ml)	CRS Status				Chi square value	P value
	CRS3		CRS 1 or CRS 2			
	n	%	n	%		
≤ 35.0	5	38	8	62	5.34	0.02
>35.0	0	0	11	100		

Table 9: Correlation of normal CA125 value after third chemo with DFS in HGSC subgroup (n=24).

CA125 value after 3 cycles neoadjuvant chemotherapy (U/ml)	DFS (in months)				Chi square value	P value
	>12 months		<12 months			
	n	%	n	%		
≤35.0	9	69	4	31	12.185	<0.001
>35.0	0	0	11	100		

Table 10: Correlation of post cytoreduction CA125 value with DFS in patients with HGSC (n=24).

Post cytoreduction CA 125 (U/ml)	DFS (in months)				Chi square value	P value
	>12 months		<12 months			
	n	%	n	%		
≤10	9	69	3	31	14.40	<0.001
>10	0	7	12	93		

Similar to overall study population patients with HGSC who have CA125 level ≤10 u/ml post interval cytoreduction have likelihood of longer disease-free survival compared to those with CA125 >10 u/ml (Table 10).

DISCUSSION

A total of 33 patients were included in the study. All the patients received neo adjuvant chemotherapy with carboplatin and paclitaxel combination, every 3 weekly for 3 cycles. 24% of the patients were in 61-65 years of age group. High grade serous carcinoma (78.8%) was the most common histology noted. 93.9% of patients were diagnosed in stage III based on clinical and imaging findings. Following surgery, patients were found to have appreciable tumour response amid viable tumour which was readily identifiable i.e. chemotherapy response score 2 (CR_2) predominantly (74%). The prognostic factors for advanced ovarian cancer include age, performance status, histology, grade and amount of residual tumour post-surgery.[11] In this study, 82% (n=27) of patients underwent cytoreduction after 3 cycles of chemotherapy, 18% were inoperable. Similarly optimal cytoreduction was feasible in 81% of patients post NACT (neo adjuvant chemotherapy) in EORTC trial and 79% of patients in CHORUS trial.[20] Response to platinum-based chemotherapy in rare subtypes like clear cell carcinoma ranges from 21-40%.[12] This study included one patient with clear cell carcinoma who was inoperable after 3 cycles of chemotherapy indicating poor platinum response. Riedinger et al first introduced the concept of CA125 bi-exponential decrease, concluding that initial half-life and decline are predictive factors for relapse free survival and overall survival.[13] Similar findings were seen in neo adjuvant setting also.[9] Retrospective study in advanced stage epithelial ovarian cancer by Kessous et al have shown that both absolute CA125 levels and relative reduction in CA125 levels after 2 and 3 cycles predicted the chance to achieve complete debulking.[14] Though the predictive role of nadir CA125 was accepted, the cut off value to determine outcomes of surgery or disease free survival has been debated with different results from each study.[15-17] Van Altena et al reported that a CA125 nadir of ≤5 UI/ml is significantly associated with both longer relapse-free survival and longer overall survival.[18] Vasudev et al used CA125 half-life as well as its regression coefficient and found both to be significantly correlated with outcome.[19] Rodriguez et al suggested that a preoperative CA125 of ≤100 u/ml may be useful in predicting optimal cytoreduction to no gross residual disease in patients treated with Neo adjuvant chemotherapy .[20] Furukawa et al found that for advanced ovarian cancer, a pre-interval debulking surgery (IDS) CA125 level less than 20 u/ml is an independent predictor of complete IDS.[6] Though complete resection of macroscopic disease is a prognostic factor in patients undergoing primary debulking surgery, it's role may not be reliable post NACT.[21] Complete or near-complete pathologic response [defined as a chemotherapy response score (CRS) of 3] was associated with significantly improved PFS (18 versus 12 months, p<0.001) and decreased risk of platinum-resistant relapse [odds ratio (OR) 0.08; p<0.001] compared with those tumours showing less in vivo chemosensitivity (CRS scores of 1 and 2). CRS is validated to be a robust and reproducible

biomarker with significant association with PFS and OS in patient with high grade serous carcinoma.[9,22] In this study it is observed that log reduction in CA125 values from the time of diagnosis till before surgery showed no correlation with disease free survival or pathological response. In subgroup analysis including patients with high grade serous carcinoma also log reduction in CA125 values from baseline to pre interval cytoreduction has not shown significantly correlation with CRS score or disease-free survival. However, the level of CA125 after third cycle of neo adjuvant chemotherapy showed significant correlation with chemotherapy response score and DFS in all the patients who were operable at the end of neo adjuvant chemotherapy. In our study it was observed that patients with normal pre IDS CA 125 value i.e., <35 IU/ml had DFS of more than 12 months which also means sensitivity to platinum based chemotherapy. Pelissier et al results suggested that advanced epithelial ovarian cancer patients who normalized their CA125 level after the third NAC cycle (<35 UI/ml), have significantly longer relapse free survival (RFS) and Overall survival (OS).[25] The value of CA125 post interval cytoreduction is not useful in predicting recurrence. Follow up CA 125 monitoring needs to be done.

However. post cytoreduction CA 125 has significant correlation with DFS. Patients with post cytoreduction CA 125 <10 IU/ml have DFS of more than 12 months. Studies examining the correlation between the change in perioperative serum CA125 levels and the extent of disease after surgery report conflicting results. This is mainly due to release of CA 125 during abdominal surgery by peritoneal trauma and handling of tumor. Also, different time lines of CA 125 testing can affect analysis. In a retrospective study by Zwakman et al suggested that the perioperative decline in serum CA125 >80% is an early biomarker that predicts disease-specific survival in patients who underwent primary cytoreductive surgery for advanced stage EOC.[23]

The probability of overall survival was 34.1%. A retrospective study of patients with advanced stage epithelial ovarian cancer showed median PFS 17.5 months with overall survival of 37% at the end of 5 years.[24] Three patients of carcinosarcoma were included in the study as they were initially reported to have high grade serous carcinoma were later changed to carcinosarcoma after further Immunohistochemistry tests or postoperatively. Few patients have not tested CA125 value after each cycle of neoadjuvant chemotherapy due to logistic reasons caused by the pandemic situation.

CONCLUSION

CA125 as a biomarker for screening, progression has been widely studied. Our study showed that CA125 levels can predict the outcome of women undergoing neo adjuvant chemotherapy followed by debulking surgery for advanced stage epithelial ovarian cancer. CA125 level more than 35 UI/ml after the 3rd NAC cycle have a high risk of relapse within 12 months. Normalisation of CA125 level before interval cytoreduction has significant positive correlation with CRS in patients with HGSC. Decline in CA125 value to less than 10 IU/ml post interval cytoreduction correlates with disease free survival in overall study population.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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