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Original Research Article

Response evaluation of locally advanced carcinoma ovary to neoadjuvant chemotherapy at a tertiary care centre

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ABSTRACT

Background: Clear cell and mucinous types of epithelial ovarian cancers are relatively chemo resistant and have a poorer prognosis compared to other histologies. Aim of the study was to study the biochemical and histopathological response and surgical outcome of various histologies to standard platin based chemotherapy.
Methods: All 42 cases of locally advanced carcinoma ovary who received several cycles of neoadjuvant chemotherapy (NACT) followed by, interval cytoreductive surgery (ICS) were included in this study. Serum CA125 levels before and after neoadjuvant chemotherapy, the ability to achieve optimal cytoreduction and the presence of residual tumour in the surgical specimen were the parameters measured. Continuous variables were compared by one-way ANOVA. Categorical variables were compared by the Pearson chi-square test. Significance was defined by p values less than 0.05. Survival analysis was done using Kaplan-Meier estimation.
Results: There was a 95,84% reduction in serum CA125 levels for papillary serous carcinoma compared to clear cell and mucinous varieties, which had 81.2% and 78.5% reduction, respectively. More number of papillary serous tumours were able to achieve optimal cytoreduction (72%) compared to mucinous variety (25%). Residual tumour was present in 68% of serous papillary tumours compared to 87.5% in mucinous and 80% in clear cell histology.
Conclusions: Our study concludes that mucinous and clear cell types of EOC are relatively chemo resistant compared to the serous subtype. We recommend more aggressive surgery especially for mucinous tumours. In the case of ovarian cancer, we observed that the mucinous and clear cell types of EOC are relatively chemoresistant compared to the serous subtype. From the results, we recommend the more aggressive strategy of surgery as a preliminary choice of treatment especially for mucinous tumours rather than chemotherapy in patients with EOC.

Keywords: Epithelial ovarian tumor, Carboplatin, Paclitaxel, CA-125, Mucinous

INTRODUCTION

Carcinoma Ovary ranks third in gynaecological cancer-related mortality among women worldwide (GLOBACON 2018). Tumour stage is considered the most important prognostic factor in ovarian cancers. Most of the ovarian cancers are diagnosed in stages III or IV. Other major prognostic factors are residual tumour volume present after cytoreductive surgery, histologic subtype, histologic grade, age and performance status.[1] About 90% of ovarian cancers are epithelial in origin.

Clear cell and mucinous types of epithelial ovarian cancers (EOC) are relatively chemo resistant [1,2,3]and hence these patients do not fare as well compared to patients with other types of cancers.

Serum CA 125 is elevated in greater than 90% of women with stage III to IV epithelial ovarian cancer.[4,5] The frequency of elevated concentrations is highest in patients with serous tumours followed by endometrioid and clear cell types.[4,5] The CA 125 is not expressed in pure mucinous tumours and is not a useful marker in this histologic subtype [4]. CA 125 level is useful in diagnosis, to assess treatment response and for post-treatment surveillance in EOCs. Markman et al. reported that a decrease in CA 125 concentrations of 50% or higher

during the initial 2 cycles of platinum-based chemotherapy was a powerful independent prognostic indicator for overall survival.[6] The Gynaecological Cancer Intergroup in 2011 reached a consensus in defining a CA 125 response as at least a 50% reduction in CA 125 levels from a pre-treatment sample, to be included in The Response Evaluation Criteria in Solid tumors for use in first-line trials in ovarian cancer.[7]

According to current guidelines, the recommended treatment for stage IA to IV is primary debulking surgery followed by six to eight cycles of platinum and taxane-based adjuvant chemotherapy provided the patient is not a poor surgical candidate and optimal cytoreduction is likely to be achieved.[8] Otherwise, platinum-based neoadjuvant chemotherapy for 3 or 4 cycles followed by interval debulking surgery followed by adjuvant chemotherapy is practiced.[8] Platinum sensitivity is very important in the treatment of advanced ovarian cancer. Tumour cell type is shown to be the most relevant histologic prognostic factor in advanced ovarian cancer treated with platinum and taxane.[9] Survival depends on the maximum diameter of residual disease left after cytoreductive surgery.[10]

This retrospective study was carried out to evaluate the biochemical and histopathological response and surgical outcome for various histologies of epithelial ovarian cancer following treatment with standard platin-based chemotherapy. The quantity of elevation of serum CA 125 levels above baseline was also compared between various histologic subtypes of epithelial ovarian cancer.

METHODS

This Retrospective study was conducted in the Department of Surgical Oncology at Tirunelveli Medical College Hospital from November 2015 to April 2019. Institutional Review Board has approved this study. Records belonging to 42 patients of locally advanced carcinoma ovary who were stage III and stage IVA, who underwent interval cytoreduction after receiving several cycles of platin based neoadjuvant chemotherapy along with paclitaxel from November 2015 to December 2017 was studied. All 42 patients were evaluated prior to receiving neoadjuvant chemotherapy with serum CA 125 levels, contrast-enhanced Computed Tomography (CT) of the chest, abdomen and pelvis and biopsy. A serum CA 125 level of <35 U/ml was considered as baseline. They were not routinely evaluated for gastrointestinal malignancies unless they had symptoms. As these patients had a serum CA 125 >500 IU/ml, poor ECOG performance status, omental cake extending to spleen, porta hepatis nodes or bulky suprarenal adenopathy in CT images, they were started on neoadjuvant chemotherapy (NACT). All of them were evaluated after three cycles with a serum CA 125 level and contrast CT of chest, abdomen and pelvis. If there was an adequate response, a cytoreductive interval surgery (ICS) was done. If not, these patients received two more cycles of chemotherapy and then underwent ICS. All patients received at least two cycles of the same chemotherapy if optimal cytoreduction was achieved. If not, they were started on second-line chemotherapy consisting of liposomal doxorubicin and bevacizumab. All patients were followed up till April 2019.

Percentage decrease in the CA 125 level after chemotherapy, the ability to achieve optimal cytoreduction and complete pathological response were the parameters measured.

Statistical analysis

Data are presented as mean, standard deviation, percentages, or number of cases. Continuous data were compared by one-way ANOVA. Categorical data were compared by the Pearson chi-square test. Significance was defined by p values less than 0.05. Data analysis was performed using IBM-SPSS version 21.0 (IBM-SPSS Science Inc., Chicago, IL). Survival analysis was done using Kaplan-Meier estimation.

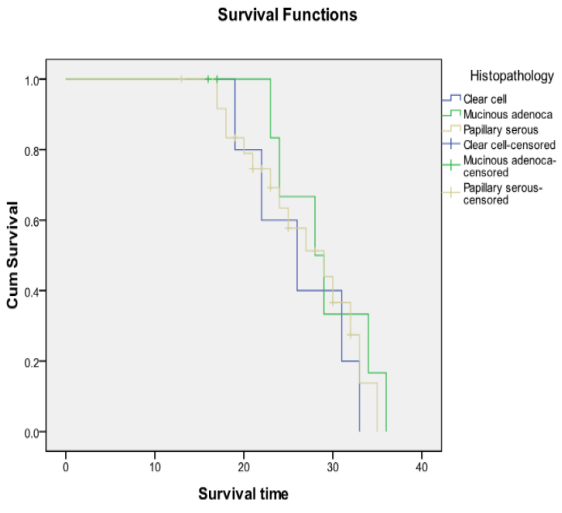

Figure 1. Kaplan-Meier Survival Curve.

RESULTS

Among the 42 cases of locally advanced ovarian cancers included in this study, 39 cases (92.9%) were epithelial ovarian cancers and the other 3 (7.1%) were granulosa

cell tumors (stromal tumours) (Table 1). Both mucinous and clear cell variety considered rare histologic subtypes accounted for 31% in our study. There was no significance in the mean age at diagnosis of various subtypes. All the serous tumours in our study were high grade.

About 71.4% of the patients (n=30) received three cycles of neoadjuvant chemotherapy, whereas another nine patients (21.4%) and three patients (7.1%) received 4 and 6 cycles chemotherapy respectively. The mean serum CA 125 levels measured for various histologic subtypes of EOC before administering neoadjuvant chemotherapy and after completing chemotherapy are shown in Table 2

As seen in [Table 2], the prechemotherapy CA 125 levels were elevated in serous subtype (mean 2645.71) compared to clear cell (mean 349.46) and mucinous (mean 268.9) reaching statistical significance with p value 0.02 for clear cell tumours and 0.002 for mucinous tumours. We had only one case of endometrioid adenocarcinoma with a CA 125 value of 239.2 IU/ml. All patients had an elevated CA 125 levels above baseline.

Most of the patients (n=30) received 3 cycles of chemotherapy before interval cytoreduction and nine and three other patients received 4 and 6 cycles of chemotherapy, respectively. In Table 3, the percentage reduction in serum CA 125 level was most marked with serous tumours after administering platin based chemotherapy with a mean of 95.84%. This reduction in CA 125 levels was only 81.2% for clear cell tumours and 78.50% for mucinous tumours reaching a statistical significance with mucinous tumours (p value =0.012) compared to serous tumours. As seen in Table 2, the post-chemotherapy CA 125 levels touched baseline (<35 U/ml) in mucinous tumours but not so in serous and clear cell varieties. This might be because of the lower pre-chemotherapy CA 125 level.

Among the 42 patients, 69% achieved optimal cytoreduction. About 72% (n=18) were able to achieve optimal cytoreduction among the 25 cases of serous tumours (Table 4). Mucinous adenocarcinoma patients fared the worst having an optimal cytoreduction rate of 25% only (2 out of 8 cases) with a p value of 0.013, which is significant. Surprising, optimal cytoreduction was achieved in all patients with clear cell carcinoma despite diminished biochemical response compared to serous tumours. Optimal cytoreduction was achieved in the single case of endometrioid adenocarcinoma. The mean CA 125 level in patients receiving optimal cytoreduction did not touch baseline in any of the histologic subtypes in our study. The reasons for not achieving optimal cytoreduction were root of mesentery infiltration, extensive small bowel involvement, lesser sac and porta hepatis involvement.

About 26.2% of cases among the total of 42 did not have any residual tumour in the post-operative specimen after interval cytoreduction indicating a complete pathological response (pCR) to chemotherapy. In this aspect also mucinous tumours and clear cell tumours fared worse with a pCR rate of 12.5% and 20% respectively compared to serous tumours with a pCR of 32%, not reaching statistical significance (p=0.49). Moreover, predictably the CA 125 level in all the histologic subtypes of EOC except the single patient with endometrioid adenocarcinoma was normal before IDS.

Table 1. Clinicopathological characteristics of various histological subtypes.

Characteristic	N	%	Mean age
Histologic subtype			
All types	42	100	54.6
Serous	25	59.5	55
Mucinous	8	19	57.5
Clear cell	5	11.9	51.6
Endometroid	1	2.4	51
Others	3	7.1	50
ECOG performance status			
1	20	47.6	
2	22	52.4	
Stage			
111	38	90.5	
IVA	4	9.5	
Histology			
Serous	25	59.5	
Mucinous	8	19.1	
Clear cell	5	11.9	
Endometroid	1	2.4	
Others	3	7.1	
Grade			
2	13	31	
3	29	69	
Menopausal status			
Pre-menopausal	9	21.4	
Post-menopausal	33	78.6	
Family history			
Yes	2	4.8	
No	40	95.2	

Table 2:CA125 levels prior to and after NACT in various histologic subtypes.

Histologic Subtype	Pre-chemo CA125 Level (U/ml)	Post-chemo CA125 Level (U/ml)
Serous	2645.71	82.18
Mucinous	268.9	31.79
Clear cell	349.46	55.54
Endometroid	239.2	42.7
Granulosa cell	171.57	37.77

Pre-chemo CA125 = CA125 level prior to NACT, Post-chemo CA125 = CA 125 level after NACT and prior to ICS.

Table 3. Percentage reduction in CA125 level after NACT in various histologic subtypes.

Histologic Subtype	Percentage Reduction in CA 125 level (pre and post chemotherapy)		
	Mean	SD	Range
Serous	95.84	5.2	77.00 -100.00
Mucinous	78.5	22.79	29.00 – 97.00
Clear cell	81.2	17.51	51.00 – 94.00

Pre-chemotherapy = CA125 levels prior to NACT
Post-chemotherapy = CA125 levels after NACT and prior to ICS.

Table 4. Correlation between optimal cytoreduction and post-chemotherapy CA125 level.

Histologic Subtype	Optimal Cytoreduction		Sub-optimal cytoreduction	
	n	Post-chemo CA 125 level (U/ml)	n	Post-chemo CA 125 level (U/ml)
Serous (n=25)	18	47.7	7	171
Mucinous (n=8)	2	41.4	6	28.6
Clear cell (n=5)	5	55.54	55.54	nil
Endometroid (n=1)	1	42.7	42.7	nil
Granulosa (n=3)	3	37.77	37.77	nil

n = no of patients
Post-chemo CA125 = CA125 level after NACT and prior to ICS

Table 5. Correlation between CA125 level and absence of residual tumour at ICS.

Histologic Subtype	Residual Tumour Present		Residual Tumour Absent	
	N	CA 125	N	CA 125
Serous (n=25)	17	109.2	8	21.8
Mucinous (n=8)	7	35.2	1	7.7
Clear cell (n=5)	4	66.3	1	12.5
Endometroid (n=1)	nil	nil	1	42.7
Granulosa (n=3)	3	37.77	nil	nil

n = no of patients; CA125 = CA 125 level after NACT and prior to ICS.

The median follow-up was 24.9 months. The median Overall Survival (OS) for papillary serous, mucinous and clear cell adenocarcinoma was 29, 28 and 26 months respectively with no statistical significance.

DISCUSSION

In our current analysis, 100% of stage III and IV patients had abnormal CA 125 levels, compared with the study by Morales-Vasquez et al. where 96% and 98% had abnormal CA 125 levels in stage III and stage IV respectively.[11] They conclude that the absolute values of pre-treatment CA 125 levels should be considered as a prognostic factor in EOC patients.

Further, the study by Morales-Vasquez et al. consisting of 1009 patients with EOC, CA 125 levels of various histologic subtypes was measured for stages I, II, III and IV prior to starting any treatment. In the above study the mean values for serous, clear cell, mucinous and endometrioid subtypes were 1255 U/ml, 415 U/ml, 195 U/ml and 861 U/ml respectively, with the highest value for serous tumours and lowest values for mucinous tumour[11]. This is in concordance with our present study.

In our present study, all varieties of EOC had more than 50% response to chemotherapy. Several studies had found that even when complete macroscopic cytoreduction was achieved at interval cytoreduction, survival was worse with more than three or four cycles of neoadjuvant chemotherapy.[12,13] Rustin et al correlated decreasing CA125 levels with response to chemotherapy.[14] In our results, both mucinous and clear cell tumours were not so responsive as serous tumours with mucinous tumours lagging behind with a significant P value proving the fact that clear cell and mucinous tumours are relatively chemoresistant.[15,16,17,18]

Poor response to chemotherapy almost always results in suboptimal cytoreduction. Suboptimal cytoreduction translates into decreased PFS and OS rates.[10] Moreover, a normal CA125 level before IDS is associated with improved survival in NACT-IDS.[19] In our study, suboptimal cytoreduction in mucinous tumours achieved statistical significance when compared to serous tumours. Surprisingly, all 5 patients with clear cell tumours achieved optimal cytoreduction despite the relative chemoresistance. This might be due to the lesser number of clear cell tumours in this study. Based on molecular and clinicopathological characteristics, EOCs are categorised in to type I and II by Kurman and Shih.[20,21] Type I includes lower grade malignancies like low grade serous, mucinous, endometrioid and clear cell varieties and Type II includes the high-grade serous type. High-grade serous tumour is characterised by p53 mutation and mucinous tumours by KRAS mutation in 40 to 50%.[21]

Ferron et al. in his study showed that pCR in the surgical specimen of interval cytoreductive surgery occurred in 14% of patients and was predictive of PFS.[22] Another

larger study, including 322 patients, also confirmed that pCR was predictive of both PFS and OS.[23]In the current study pCR rate was less in clear cell and mucinous tumours compared to high-grade serous tumours, confirming the relative chemoresistance of clear cell and mucinous tumours.

In the study by Winter et al, the median OS for serous, mucinous and clear cell tumours was 45.1, 14.8 and 24 months respectively.[1] In the present study, there was no statistically significant difference in OS among the various subtypes of EOC.

Both clear cell and mucinous carcinomas are rare in the advanced stages and together constitute 5-8% of EOCs in various studies.[24] In our study, these two histologies constituted about 31%. Inaccurate diagnosis of a gastrointestinal malignancy as ovarian primary can occur even in a trial where specimens are viewed centrally to confirm the diagnosis as in the GOG study by Tian et al.[24] In their study, they also state that studies on mucinous and clear cell tumours are difficult due to their limited numbers and requires a meta-analysis.[24] Our study is also limited by a smaller number of cases.

CONCLUSION

Our study concludes that mucinous and clear cell types of EOC are relatively chemoresistant compared to the serous subtype. We recommend more aggressive surgery, especially for mucinous tumours. Currently, there is a consensus among medical fraternity that the standard platinum and taxane doublet is more suitable for high-grade serous tumours and is ineffective for mucinous tumours. Multicentre GOG 241 trial [25] randomised patients with mucinous ovarian cancer to standard platin doublet arm or capecitabine and oxaliplatin arm as for gastrointestinal malignancies. Unfortunately, they could not accrue the enough patients as they conclude that mucinous tumours are rarer than previously thought. So, there is a need for studies focussed on developing therapeutic agents for primary mucinous adenocarcinoma of ovary based on molecular targets.

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