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Research Article

ASSESSMENT OF COMPLETE CLINICAL RESPONSE RATE AFTER CHEMOTHERAPY IN ADVANCED EPITHELIAL OVARIAN CANCER

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A B S T R A C T

Current study was designed to determine the complete clinical response rate of chemotherapy in advanced epithelial ovarian cancer and a subgroup analysis of chemotherapy response in neoadjuvant chemotherapy approach and primary debulking surgery followed by chemotherapy approach. Study was conducted in prospective and cross sectional manner. This study was conducted in Clinical oncology Department JPMC, Karachi from 14 Jan 2016 to 13 Jan 2017. Seventy three (73) patients meeting the inclusion criteria were enrolled in study after complete staging workup. Out of them 40 patients received initial suboptimal debulking surgery followed by 6 cycles of chemotherapy with an interim treatment response after 3 cycles. A group of 27 patients received neoadjuvant chemotherapy 3 cycles followed by interval debulking surgery and then 3 cycles of adjuvant chemotherapy. Complete clinical response was identified in 18 (27%) while 28 (42%) were identified as partial response, stable disease was 14 (21%) and 7(10%) were with progressive disease. Complete clinical response in primary debulking surgery group was 37.5% (15/40) and partial response was 32.5 % (13/40). In Neoadjuvant chemotherapy group, complete clinical response was found 11.11% and partial response was found 55.5 %. Results showed no significant differences in treatment responses according to stages in debulking (p-value=0.147) and interval surgery groups (p-value=1.000). There is statistically no difference in both treatment strategies in terms of response outcomes.

INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the most lethal gynecological malignancies. Worldwide, it ranks 7th among all cancers and 8th most common cause of cancer related deaths in women (Lee *et al*., 2016). In 2017, in USA 22,440 new cases and 14,080 deaths are reported in ovarian cancer. According to surveillance, epidemiology and end results program of the National cancer institute (SEER) data 2017 healthy population risk of getting ovarian cancer is 1.3 % throughout their lives (Rebecca *et al*., 2017). Epithelial ovarian cancer is actually a disease of delayed diagnosis usually presents in late 50s because of nonspecific symptoms and lack of proper early detection screening programmes. Up to 60 % epithelial ovarian cancer presents with advanced stage III and IV and having different response to treatment depending on histological subtype, grade and clinical stage (Rebecca *et al*., 2017; Camean *et al*., 2016).

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Treatment modalities for advanced epithelial ovarian cancer include surgery and taxane and platinum based chemotherapy. Standard approach is Upfront debulking Surgery for locally advanced resectable tumor from stage IIB to III as per surgeon expertise followed by chemotherapy. If tumor burden is high with widespread disease, patient unfit for surgery and tumor was found unresectable e.g., stage IV then chemotherapy is initial treatment modality followed by surgery depending on response to chemotherapy (Camean *et al*., 2016). But now a day's Neoadjuvant chemotherapy followed by interval debulking surgery is gaining popularity as first line as it potentially downstage the tumor in wide spread disease, improves surgical outcome, decreases morbidity and intraoperative blood loss (Huober *et al*., 2002).

Epithelial ovarian cancer is one of the most chemo sensitive solid tumors having response up to 80%. In Gynecology Oncology Group 111, response of chemotherapy was checked it showed 43% and 23% complete response and Partial response in epithelial ovarian cancer (Muggia *et al*., 2000). In another study Baruah at el., described response of chemotherapy was 18% complete response and 76% partial response (Baruah *et al*., 2015).

The primary aim of this study was to determine the complete clinical response rate of chemotherapy in advanced epithelial ovarian cancer (EOC) in local population and to compare the results with international studies. The secondary aim of this study was to find out better treatment arm between primary debulking surgery followed by chemotherapy (PDS- CT) and neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) in terms of response to chemotherapy. No such studies have been mentioned on National level, which necessiates the findings of such parameters in our cohort.

MATERIAL AND METHOD

Patients and Methods: This is a cohort study which was conducted in Clinical oncology Department JPMC, Karachi from 14 Jan, 2016 to 13 Jan 2017 after Approval from institutional Ethic review committee. (Reference no: 34676 dated: 18-01-16). Written informed consent was taken from all enrolled patients.

Sample Size Calculation

Sample size is calculated with the help of WHO sample size calculator. By taking expected 5.5% desired level of absolute precision (d) for 95% confidence interval with 5% level of significance. Sample size was found to be 57 which were inflated up to 73 to exclude the non respondent cases.

$$n = \frac{1.96^2\, p(1-p)}{d^2} = \frac{1.96^2 \times 0.82 \times (1-0.82)}{(0.1)^2} = 57$$

Inclusion criteria

- Histopathological confirmed, advanced Epithelial ovarian cancer with FIGO stage III and IV with at least >1 cm measureable disease on scans.
- ECOG performance status (0-2)
- Good renal and liver function tests
- The patients who had not received any prior anticancer treatment(chemotherapy and radiotherapy)

Exclusion criteria

- Patients with non epithelial histology ovarian cancer were excluded
- ECOG performance status 3-4

1. Patients who had recurrent ovarian cancer
2. The patients who denied chemotherapy

The pre-treatment work-up was based on thorough history and physical examination including per abdominal and per-vaginal examination. Diagnosis was established on tissue biopsy taken via surgery or ultrasound (USG) guided technique. Metastatic workup included chest CT scan and Abdomino-pelvic CT/MRI. International federation of gynecology oncology staging system (FIGO) was used to stage the tumor according to clinical and radiological findings. Pleural effusion and ascites were drained diagnostically for cytological examination to proper stage the disease and therapeutically drained in 20 patients before starting chemotherapy, so that no third space accumulation of chemotherapeutic drug in pleural and peritoneal cavity that could lead to decrease in effective circulating dose of drug. Complete blood counts, blood chemistry including liver and renal function test, serum electrolytes, Ca 125 levels, viral markers screening and ECG was done. A total of 73 patients meeting the inclusion criteria were enrolled in study after complete staging workup and 67 patients had final treatment response assessment. Every patient was discussed with gynecological surgeon to decide treatment plan and timing and possibility of complete cytoreductive surgery. Of them 40 patients have initial suboptimal debulking surgeries with post op residual disease >1 cm on CT/MRI scans and followed by 6 cycles of chemotherapy. While 27 patients had received neoadjuvant chemotherapy 3 cycles followed by surgery after observing post chemotherapy response and received 3 more cycles of chemotherapy after surgery. All these patients have measureable disease at the time of starting chemotherapy regimen. A large no of suboptimally debulked surgeries can be explained on the basis of unavailability of gynecological oncological expertise, lack of intraoperative frozen section facility and long waiting list that may delayed the treatment and leading towards disease progression.

Study treatment

Treatment regimens were combination chemotherapy consisting of Carboplatin with AUC 6with 1 hour infusion Paclitaxel with 175 mg/m^2 with 3 hour infusion Q x Every three weekly with total 6 cycles were planned.

Carboplatin dosing calculation

Dose [mg]= Target AUC X[creatinine clearance +25].
Premedication included oral dexamethasone 20 mg at 12 and 6 hours before the infusion or 20 mg intravenously 30 minutes before the paclitaxel infusion. Diphenhydramine 50 mg and cimetidine 300 mg both were administered intravenously 30 minutes before the paclitaxel infusion. In this study 40 patients completed 6 cycles chemotherapy after primary debulking surgery and 27 patients completed 3 cycles of neoadjuvant chemotherapy and remaining 3 cycles after interval debulking surgery. Post chemotherapy response assessment was done with CT/MRI after 15 days of 6 cycles however an interim CT/MRI scan was done after 3 cycles to check the chemotherapy response. If patient disease was found progressive after interim analysis then they were switched to second line chemotherapy. In neoadjuvant chemotherapy group response assessment was done after 3 cycles of chemotherapy before surgery and remaining 3 cycles were given in adjuvant settings. Response assessment was done according to Response evaluation criteria for solid tumors (RECIST) version 1.1. No comparison of response assessment was done between 2 treatment arms because this study was not double blind randomized controlled trial in which all study variables were balanced and compared in 2 treatment groups. Rather this is an observation analysis about response of chemotherapy in 2 different treatment scenarios in our population.

During whole course of treatment patients were followed every weekly for any subjective complaints along with clinical examination. Patients must have had an absolute neutrophils count 1,500/L and platelets more than 100,000/L before receiving the next course of therapy. Every patient above 55 years was given G-CSF support (if count is less than 1000/L after 14 days of last chemo or patient had developed fever with counts less than 1000 /L with decreasing trends to prevent the delay in further chemotherapy cycles.

Statistical analysis

Data was analyzed by using SPSS version 21.0. Descriptive statistics for patient characteristics i.e. age was reported as mean and standard deviation and CA125 level was reported as median and interquartile range because of CA125 level does not follow normality, while frequencies and percentages were reported for all categorical characteristics of patient i.e. presenting complaints (abdominal distension, abdominal pain, prevaginal bleeding, weight loss), family history, type of histology, tumor grade, clinical stage, cycles of chemotherapy, type of surgery. The outcome treatment responses (complete, partial, progressive and stable) were presented in the form of graph like pie-chart. One way ANOVA and Kruskal Wallis test were used to assess the difference of age and CA125 level with treatment response in terms of (complete, partial, stable, progressive response). Fisher's exact test was used to examine the association of confounding patient characteristics according to response of treatment. Further, stage wise differences with treatment response according to debulking and interval type of surgery were also assessed using Fisher's exact test. A value of $p<0.05$ was considered significant.

RESULTS

A total of 67 cases of epithelial ovarian carcinoma patients were included in the study. The mean age of the patients was 45.57±10.810 years. The median (inter-quartile rang) of CA125 level was 1200 (2450). Chemotherapy protocol includes paclitaxel 175mg/m^2 IV and carboplatin with AUC x 6 and repeated after every 3 weeks. Sixty seven patients have post treatment response assessment with CT/MRI scan after 14 days of last chemotherapy. Response assessment was done according to RECIST criteria *vs* 1.1 A total of 67 cases of advanced epithelial ovarian cancer patients were included in the study Mean age of the patients was 45.57±10.810 years SD. Regarding presenting complaint of the ovarian carcinoma, 28 (41.8%) were abdominal distension, 52 (77.6%) was abdominal pain, 12 (17.9%) was prevaginal bleeding while 2 (3.0%) were weight loss. The family history was positive in 5 (7.5%) patients. The most reported type of histology was serous 39 (58.2) while least reported type was clear cell 4 (6%). The G3 tumor grade 53 (79.1%) was found to highest. Clinical stage was almost similar 33 (49.3%) in Stage 3 and 34(50.7%) in Stage 4. The 3 cycles of neoadjuvant chemotherapy was reported in 32 (47.8%) patients while 6 cycles were reported in 35 (52.2%). The debulking surgery was reported in 40 (59.7%) while interval surgery was reported in 27 (40.3%) (Table 1). Complete clinical response was identified in 18 (27%) while 28 (42%) were identified as partial response, stable disease was 14 (21 %) and 7(10%) were with progressive disease (Table 2).

The mean age was also assessed in terms of treatment response, which was 42.50±11.77 years in complete response, 44.36±10.65 years in partial response, 51.50±9.16 years in stable disease while 46.43±9.07 years in progressive disease. The median (inter-quartile range) of CA125 level was 633 (3076) in complete response, 1763 (2819) years in partial response, 1172 (1610) years in stable disease while 870 (885) years in progressive disease. There were no significant differences were observed regarding age (p-value=0.106) and CA125 level (p-value=0.177) in terms of treatment response. There was no association of treatment response was observed with presenting complaints includes abdominal distension (p-value=0.365), abdominal pain (p-value=0.418), prevaginal bleeding (p-value=0.825) and weight loss (p-value=0.095), family history (p=0.339), type of histology (p=0.494), tumor grade (p=0.499), clinical stage (p=0.086), type of surgery (p=0.06), There is an association of treatment outcome was observed with cycles ($p<0.05$) (Table 2). Treatment outcome was stratified for type of surgery i.e. debulking and interval. For debulking surgery group, the treatment responses were reported as complete response 12 (80%), partial response 9 (69.2%), stable disease 3 (33.3%) and progressive disease 2 (66.7%) in stage 3 while in stage 4, the treatment responses were reported as complete response 3 (20%), partial response 4 (30.8%), stable disease 6 (66.7%) and progressive disease 1 (33.3%). For interval surgery group, the treatment responses were reported as complete response 1 (33.3%), partial response 4 (26.7%), stable disease 1 (20%) and progressive disease 1 (25%) in stage 3 while in stage 4, the treatment responses were reported as complete response 2 (66.7%), partial response 11 (73.3%), stable disease 4 (80%) and progressive disease 3 (75%). Results showed no significant differences in treatment responses according to stages in debulking (p-value=0.147) and interval surgery groups (p-value=1.000) (Table 3).

Table 1 Patient Characteristics of Ovarian Carcinoma (n=67)

Characteristics		n=67
Age (years)	**Mean±SD**	45.57±10.810
CA125 level	**Median (IQR)**	1200 (2450)
		n (%)
Abdominal Distension		
	Yes	28 (41.8)
	No	39 (58.2)
Abdominal Pain		
	Yes	52 (77.6)
	No	15 (22.4)
Pervaginal Bleeding		
	Yes	12 (17.9)
	No	55 (82.1)
Weight Loss		
	Yes	2 (3.0)
	No	65 (97.0)
Family History		
	Yes	5 (7.5)
	No	62 (92.5)
Type of Histology		
	Endometriod	6 (9.0)
	Mucinous	8 (11.9)
	Serous	39 (58.2)
	Clear Cell	4 (6.0)
	Poorly Differentiated	10 (14.9)
Tumor Grade		
	G1	8 (11.9)
	G2	6 (9.0)
	G3	53 (79.1)
Clinical Stage		
	Stage 3	33 (49.3)
	Stage 4	34 (50.7)
Number of Cycles		
	3	32 (47.8)
	6	35 (52.2)
Surgery		
	Debulking	40 (59.7)
	Interval	27 (40.3)

A total of 73 patients sample was enrolled initially. Out of them 67 patients had post chemotherapy response assessment and they had completed their treatment without any modification. Two patients were referred to best supportive care after cycle 2 due to decrease in ECOG status. While two patients quit treatment. In one patient chemotherapy was hold

due to hydronephrosis and renal failure. one patients died without taking any treatment.

Table 2 Correlation of Study Variables and Treatment Outcome (n=67)

Characteristics		Complete Response	Partial Response	Stable Disease	Progressive Disease	
		n=18 (26.8%)	n=28 (41.7%)	n=14(20.8%)	n=7 (10.4%)	
		Mean±SD	Mean±SD			p-value*
Age (years)		42.50±11.77	44.36±10.65	51.50±9.16	46.43±9.07	0.106
CA125 level		633 (3076)	1763 (2819)	1172 (1610)	870 (885)	0.177
		n(%)	n(%)	n(%)	n(%)	p-value*
Abdominal Distension						
	Yes	5 (27.8)	15 (53.6)	5 (35.7)	3 (42.9)	0.365
	No	13 (72.2)	13 (46.4)	9 (64.3)	4 (57.1)	
Abdominal Pain						
	Yes	14 (77.8)	24 (85.7)	9 (64.3)	5 (71.4)	0.418
	No	4 (22.2)	4(14.3	5 (35.7)	2 (28.6)	
Paravaginal Bleeding						
	Yes	3 (16.7)	4 (14.3)	3 (21.4)	2 (28.6)	0.825
	No	15 (83.3)	24 (85.7)	11 (78.6)	5 (71.4)	
Weight Loss						
	Yes	0 (0.0)	0 (0.0)	1 (7.1)	1 (14.3)	0.095
	No	18 (100.0)	28 (100.0)	13 (92.9)	6 (85.7)	
Family History						
	Yes	3 (16.7)	2 (7.1)	0 (0.0)	0 (0.0)	0.339
	No	15 (83.3)	26 (92.9)	14 (100.0)	7 (100.0)	
Type of Histology						
	Endometriod	2 (11.1)	1 (3.6)	1 (7.1)	2 (28.6)	0.494
	Mucinous	3(16.7)	3 (10.7)	2 (14.3)	0 (0.0)	
	Serous	12 (66.7)	15 (53.6)	9 (64.3)	3 (42.9)	
	Clear Cell	0 (0.0)	3 (10.7)	1 (7.1)	0 (0.0)	
	Poorly Differentiated	1 (5.6)	6 (21.4)	1 (7.1)	2 (28.6)	
Tumor Grade						
	G1	3 (16.7)	3 (10.7)	2 (14.3)	0 (0.0)	0.499
	G2	2 (11.1)	1 (3.6)	1 (7.1)	2 (28.6)	
	G3	13 (72.2)	24 (85.7)	11 (78.6)	5 (71.4)	
Clinical Stage						
	Stage 3	13 (72.2)	13 (46.4)	4 (28.6)	3 (42.9)	0.086
	Stage 4	5 (27.8)	15 (53.6)	10 (71.4)	4 (57.1)	
Number of Cycles						
	3	3 (16.7)	15 (53.6)	10 (71.4)	4 (57.1)	0.01*
	6	15 (83.3)	13 (46.4)	4 (28.6)	3 (42.9)	
Surgery						
	Debulking	15 (83.3)	13 (46.4)	9 (64.3)	3 (42.9)	0.06
	Interval	3 (16.7)	15 (53.6)	5 (35.7)	4 (57.1)	

* p-value calculated by using Anova test (Age), Kruskal Walli's test (Ca125 level)
* p-value calculated by using Fisher's Exact test

Table 3 Correlation of Stage and Treatment Outcome according to Type of Surgery (n=67)

Characteristics		Complete Response	Partial Response	Stable Disease	Progressive Disease	
		n(%)	n(%)	n(%)	n(%)	p-value*
Debulking	Stage	n=15	n=13	n=9	n=3	
	3	12 (80.0)	9 (69.2)	3 (33.3)	2 (66.7)	0.147
	4	3 (20.0)	4 (30.8)	6 (66.7)	1 (33.3)	
Interval	Stage	n=3	n=15	n=5	n=4	
	3	1 (33.3)	4 (26.7)	1 (20.0)	1 (25.0)	1.000
	4	2 (66.7)	11 (73.3)	4 (80.0)	3 (75.0)	

* p-value calculated by using Fisher's Exact test

DISCUSSION

Women with epithelial ovarian cancer presents with advanced stage (FIGO III and IV) having poor treatment outcome and 5 year survival < 30 % (Romanidis *et al*., 2014). In the last three decades different chemotherapy regimens are tested for improving survival outcome. Initially cyclophosphamide and cisplatin containing regimens with or without doxorubicin combinations are used (Omura *et al*., 1989). But now carboplatin and paclitaxel regimen is approved as backbone chemotherapy in first line (Neijt *et al*., 2000; Ozole *et al*., 2003).

Epithelial ovarian cancer is chemo-sensitive tumor having both treatment options with chemo either in neoadjuvant setting or after suboptimal surgery. Outcome of surgery is very important in determining survival outcome. Survival is inversely related to post op residual tumor burden. Optimal surgery (R0) is associated with better survival as compared to suboptimal surgery R1 (<1 cm post op residual disease) 64 months *vs* 30 months (Winter *et al*., 2008). Surgery includes proper surgical staging and cytoreduction. standard surgical staging consists of, total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, total omentectomy, inspection of all abdominal organs and

peritoneal surfaces, sampling of suspicious areas for biopsy, pelvic and paraaortic lymphadenectomy (Vitale *et al*., 2013). Neoadjuvant chemotherapy (NACT) has proven clinical benefits in shrinkage of tumor with decrease in intra-tumor blood supply, decreases the periopertive morbidity and mortality, improves the quality of life, and helps in selection of platinum resistant patients. Drawback associated with NACT is formation of fibrosis and adhesions and lead to difficulty in perioperative visualization of tumor (Sato *et al*., 2014). Clinical trials have shown non inferiority of primary debulking surgery followed by chemotherapy to neoadjuvant chemotherapy followed by interval debulking surgery as management option for patients with advanced stage IIIC or IV. Van Der Burg *et al*. 1995, described median overall survival 20 months *vs*. 26 months respectively furthermore, Rose *et al*. also described median overall survival 33.7 *vs*. 33.9 months respectively and Vergote *et al*. 2010 study showed same results 30 *vs*. 29 months respectively for PDS and IDS. (Van Der Burg *et al*. 1995; Rose *et al*., 2004; Vergote *et al*. 2010).

In this study post chemotherapy complete clinical response (cCR) was found in 27%, partial response (PR) was found in 42 %, stable disease (SD) was found in 21 % and progressive disease (PD) was found in 10%. Subgroup analysis have shown complete clinical response in primary debulking surgery (PDS) group was 37.5% (15/40) and partial response was 32.5 % (13/40). Yahara *et al*., study was published in 2012 in journal of radiation research. According to this study a total of 48 patients with ovarian cancer were treated. Twenty (74%) of the 27 patients received systemic chemotherapy for the treatment of a limited recurrent tumor followed by definitive RT. Twenty-two (82%) patients had an objective response (CR: 11, PR: 11). Similar results were found in intergroup trial showing complete clinical response 41% after suboptimal debulking surgery (Piccart *et al*., 2000). In Gynecology Oncology Group 111 trial clinical complete response (cCR) was 43% and partial response (PR) was 23 % (Muggia *et al*., 2000).

In presented study, Neodjuvant chemotherapy group cCR was found 11.11% and PR was found 55.5 %. In an Indian study by Baruah *et al*., cCR was reported 18 % and PR was 76% (Baruah *et al*, 2015) and in another European study Filomenao *et al.,* described neoadjuvant chemotherapy response .it was 2.2 % cCR and 73.5 % PR (Mazzeo *et al*., 2003). In another study Yansequer *et al*., described post chemotherapy cCR was 9% and partial response PR was 71% (Ansquer *et al*., 2001). The lower response rates in our study can be explained on the basis of greater no of stage 4 patients 50 %, higher percentage of grade III histology's as compared to other studies having more percentage of stage 3 patients and mostly with grade I and grade II histology's. Most of our patients presented in advanced stage with greater percentage of poorly differentiated histology's (Table 1). Clinical trials have proven the role of chemotherapy in management of advanced EOC. There is no statistically significant proven benefit in both approaches either in neoadjuvant chemotherapy followed by interval debulking (NACT –IDS) or primary debulking surgery followed by chemotherapy (PDS-CT) in terms of overall survival (OS) benefits. Our study is first Pakistani study to address about the post chemotherapy clinical response in our population. But there is a need to conduct large randomized clinical trials to categorize the chemotherapy response, progression free survival (PFS) and overall survival (OS) in both treatment arms e.g., primary debulking surgery followed by chemotherapy and in neoadjuvant chemotherapy followed by interval debulking surgery.

CONCLUSION

Advanced epithelial ovarian cancer is lethal disease, which need to be managed aggressively both by means of surgery and chemotherapy. There is statistically no difference in both treatment strategies in terms of response outcomes. This is the need of time to find out prognostic and predictive biomarkers which are responsible for low clinical outcome in our population. Studies are also needed for proper awareness and screening programs to diagnose epithelial ovarian cancer at early stages and for proper management.

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