Original Article

Neoadjuvant Chemotherapy in Ovarian Cancer

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Objective: The primary objective of the study was to compare the efficacy and safety of adjuvant chemotherapy (ACT) with neoadjuvant chemotherapy (NACT) in patients with ovarian epithelial cancer (OEC).

Place & Duration of Study: This Randomized Controlled Trial was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore (Pakistan). Patients were enrolled and treated over one year from August 2008 to July.2009.

Patients & Methods: Total of 31 patients with advanced ovarian cancer who were selected by consecutive (non probability) sampling were divided into 2 groups to receive platinum-based chemotherapy in either adjuvant (n = 14) or neoadjuvant setting (n = 17). Efficacy was determined using radiological, pathological and biochemical (CA-125) response rates at the completion of treatment. Adverse effects of chemotherapy were noted to assess the safety of therapy.

Results: Patients in ACT arm showed superior radiological (92.9% vs. 54.4%, p = 0.039) and pathological (64.3% vs. 11.8%, p = 0.001) response rates as compared to patients in NACT arm. Higher number of patients in ACT arm were able to have optimal cytoreductive surgery than in NACT arm, but this could not reach statistical significance (85.7% vs. 76.4%; p = 0.664), probably due to small study population size. Biochemical response rates were better in NACT group (94.1% vs. 84.7%; p = 0.564). Both hematological and non-hematological adverse effects were higher in women treated with NACT.

Conclusion: Use of ACT is more efficacious and safe for patients with ovarian epithelial cancer as compared to NACT.

Key Words: *Ovarian Neoplasms; Antineoplastic Combined Chemotherapy Protocols; Adjuvant Chemotherapy; Neoadjuvant therapies*

Introduction

Ovarian epithelial cancer (OEC) is the 5th leading cause of cancer-related deaths among women in America where it accounts for 3% of all women cancers. In 2008, over 21 thousand new cases of ovarian cancer were diagnosed in the United States and about 15 thousand women died of that disease. [1] From the currently available limited information, it is estimated that ovarian cancer is the fourth most common cancer among females in Pakistan. [2] Ovarian epithelial cancer (OEC) is a silent killer as most patients experience no symptoms while disease continues to progress.[3] As a result, most patients actually present at an advanced stage, thus resulting into high mortality.[4] The optimal cytoreductive surgery (OCRS) followed by adjuvant chemotherapy (ACT) is currently considered the standard treatment for advanced OEC in many centers.[5]

There is an inverse relationship between survival and amount of residual disease after surgical resection. Only OCRS, defined as less than 2 cm residual tumor after surgical debulking, has shown survival benefit in published trials.[5] Upfront OCRS is often difficult to achieve in advanced ovarian cancers due to the large tumor bulk. Most of these patients will relapse and die of their disease, making role of upfront surgery questionable in this setting. [6, 7]

In order to achieve optimal cytoreduction in patients with advanced disease, the strategy of *interval cytoreduction* has been introduced. Interval cytoreduction involves repeating an attempt at debulking surgery after several cycles of chemotherapy, when optimal cytoreduction is not possible due to bulky disease. With the use of platinum-based chemotherapeutic regimens, response rates as high as 80% have been reported.[8] After use of adjuvant chemotherapy in patient with residual disease, OCRS was possible in 50 to 90% patients.[9] This concept has evolved into the development of neoadjvuant

chemotherapy (NACT) where an initial attempt at surgical cytoreduction is abandoned in favor of chemotherapy. The idea is to reduce the tumor burden and improve the functional status of the patients, making optimal cytoreduction easier. [6,8]

Another study published the results of first series on NACT with encouraging results.[10] It was followed by more than 20 small retrospective and prospective phase I and II studies resulting in dramatic clinical responses and despite concerns, progression-free survival and overall survivals were not compromised.[6] European Organization for Research and Treatment of Cancer (EORTC) is conducting a phase III trial in which platinum-based chemotherapy is being compared in adjuvant and neoadjuvant settings. [11] The results of this trial will help in better understanding of the management of advanced OEC.

The only documentation of use of NACT in an advanced OEC in our country was a case report describing a positive outcome.[12] However our study will be the first of its kind as a Randomized Control trial from Pakistan, comparing the results of ACT with NACT in advanced OEC.

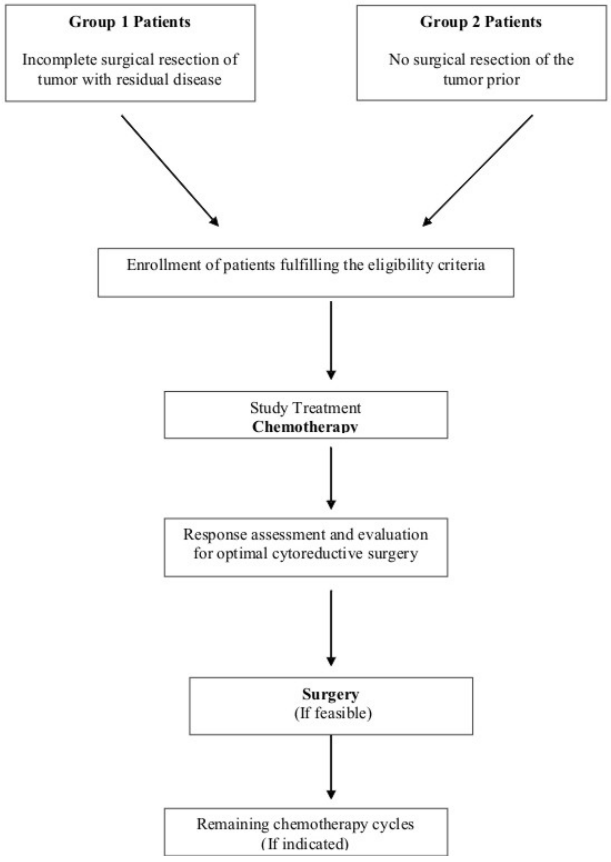
Materials and Methods

Consecutive (non-probability) sampling was employed to select the patients for this Randomized Control Trial. Patients were divided into 2 groups. Before enrollment in the study, all patents in *group 1* had some form of surgical tumor resection, leaving behind radiologically measurable disease. This residual disease was considered baseline for further treatment. *Group 2* included patients who had: (1) no previous surgery; (2) open-and-close surgical procedure with no attempt at tumor resection; (3) open surgical (core) biopsy. After enrollment in the study, chemotherapy was administered in both groups which were followed by response evaluation and definitive surgical procedure where feasible. Chemotherapy in group 1 *adjuvant chemotherapy* (ACT) and in group 2 was referred as *neo-adjuvant chemotherapy* (NACT). Study design is

Patients with following characteristics were considered eligible for the trial:

Inclusion criteria: (1) age 18 years or older (2) pathologically confirmed OEC (3) radiologic evidence of irresectable or advanced disease as evidenced by extensive omentoperitoneal involvement, absence of planes for resection, and/or presence of liver metastasis or pleural effusion (4) adequate hematologic function, defined as absolute neutrophil count (ANC) ≥1,500/µL and platelet (PLT) count ≥100,000/µL (5) adequate renal function, defined as creatinine ≤1.5 times the institutional upper limit of normal (ULN); (6) adequate liver function (LFT), defined as bilirubin ≤1.5 times the ULN and as serum alanine (ALT) and aspartate (AST) aminotransferases ≤2.5 times the ULN (7) neuropathy no more than grade 1 as defined by the revised National Cancer Institute's common toxicity criteria (NCI-CTC) version 2, grading system. [13]

Figure I: Study Design



Exclusion criteria: (1) prior treatment with any form of chemotherapy or radiation therapy (2) evidence of metastatic disease to the brain or meninges (3) recurrent/relapsed disease after optimal cytoreductive surgery for OEC.

All patients provided written informed consent for chemotherapy and surgery.

Surgical Procedures: If surgical procedure included total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAH/BSO), total omentectomy, peritoneal biopsies and peritoneal fluid sampling, lymph node dissection if nodes were palpable and resection of any other visible disease less than 2 cm, it was called optimal cytoreductive surgery (OCRS). If any of the above surgical steps was not possible leaving behind some visible residual disease more than 2 cm then the procedure was called sub-optimal cytoreductive surgery (SCRS).

Treatment with Chemotherapy: Each treatment cycle

consisted of carboplatin (area under concentration curve or AUC = 5) administered as an intravenous (iv) infusion over 30 minutes and paclitaxel 175mg/m2 administered as an iv infusion over 3 hours. The chemotherapy cycle was repeated after every 21 days. Premedication included dexamethasone 20mg orally given 12 and 6 hours prior to paclitaxel infusion.

The patients who developed severe hypersensitivity reaction to paclitaxel received only single agent carboplatin at AUC of 7 during subsequent cycles.

In patients with pre-existing peripheral neuropathy, docetaxel was administered in place of paclitaxel at dose of 100 mg/m2 IV over one hour in combination with carboplatin. Premedications before docetaxel included dexamethasone 8 mg twice a day starting a day prior to chemotherapy and continued at the same dose for next 2 days. This chemotherapy regimen was also repeated after every 21 days.

Eligible patients received up to maximum of 6 cycles of chemotherapy following which they were referred for surgery. Referral for surgery before completion of 6 chemotherapy cycles was allowed on the discretion of treating physician. Remaining chemotherapy cycles were administered after the surgical procedure.

Evaluation and Outcomes: Pre-treatment evaluation included history, physical examination, complete blood counts (CBC), LFT and serum creatinine and CA-125 levels. Diagnosis of OEC was made by image-guided fine needle aspiration (FNA) or core biopsy, biopsy taken through open surgical procedure or examination of ascitic or pleural fluid for malignant cells. Baseline chest, abdominal and pelvic radiologic images were taken not more than 28 days before start of therapy. Imaging modalities included ultrasound, computed tomography (CT scan) or magnetic resonance imaging (MRI). To achieve uniformity, all the pathological specimens and radiological films were reported by the same pathologist and radiologist respectively.

Clinical evaluation (including) assessment for chemotoxicity and blood tests (CBC, LFT and serum creatinine) were performed before start of each cycle. Serum CA-125 levels and CT scan abdomen and pelvis were repeated after every 3 cycles of chemotherapy. If due to some reason as specified above, patient was sent for surgery earlier than the planned number of chemotherapy cycles, both serum CA-125 and CT scan abdomen and pelvis were repeated earlier and patient was assessed for surgery. All the adverse effects were graded according to the NCI-CTC version 2.0. 13

Response was evaluated for efficacy after the completion of chemotherapy cycles. It was defined in terms of biochemical, radiological and pathological control of the disease and reported as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Biochemical response was evaluated by reduction in serum CA-125 at the end of chemotherapy when compared with pre-chemotherapy levels and defined as: normalization of CA-125 (CR), more than 50% reduction in the levels (PR), less than 50% reduction in CA-125 or no change in the levels in CA-125 (SD) and increase in CA-125 (PD). Radiological response was assessed by reduction in the disease burden radiologically. It was done by end of chemotherapy CT scan using Response Evaluation Criteria in Solid Tumors (RECIST).[14] Pathologic response was shown by amount of necrosis/fibrosis (negative for malignancy) vs. residual malignant disease (positive for malignancy) in the surgical specimen. It was defined as: both omentoperitoneal and pelvic specimens negative for malignancy (CR), omentoperitoneal specimen negative but pelvic specimen positive for malignancy (PR) both omentoperitoneal and pelvic specimens positive for malignancy (SD). Pathologic response was determined only in patients who underwent cytoreductive surgery.

Statistics: It is Randomized Control trial in which response to NACT was compared with that of ACT, in terms of Biochemical, radiological, and pathological response.

Sample Size Calculation: Using WHO sample size calculator for two population proportion (two sided test), where level of significance = 5%, Power of the test = 90, Anticipated population proportion (P1) = 50%9 (lit. Review), P2 = 10%,

Sample Size = 30 patients.

Two-sided Pearson's Chi-square $\chi 2$ test was used to determine differences in the baseline characteristics and the treatment administered in both randomized groups. Patients who had received atleast one cycle of systemic chemotherapy were included in the analysis.

Fisher's exact test was used to compare the response proportions in each treatment arm. Study safety parameters included adverse events (grade 3 and 4 hematological toxicities, transfusion support, febrile neutropenia, gastrointestinal and neurotoxicity) and the subsequent delays in chemotherapies. With each patient, worst-grade toxicity over all cycles was used in calculating difference in the two groups by using the Fischer's exact test.

Results

Between September, 2008 and October, 2009, 31 patients with advanced OEC were treated in our hospital with chemotherapy followed by surgery. Patients were randomly selected for either group 1 or 2 by lottery method. Patients in group 1 (n = 14) received

64 cycles of ACT followed by evaluation for interval cytoreductive surgery. Group 2 (n = 17) patients received 81 chemotherapy cycles in NACT settings. Median age was higher in group 2 patients (57) with range 27-65, as compared to 50 in group 1 with range of 28-61. Almost two-third women were post-menopausal. Patients getting ACT when compared to those getting NACT had better performance status and lesser overall disease burden. However, these differences were not statistically significant.

Table I: Efficacy of Chemotherapy in terms of Response Rates

Response†	Group 1 Adjuvant chemotherapy		Group 2 Neoadjuvant chemo		
	No.	%	No.	%	2-Tail : p-value
Biochemical Responses					
No. of patients assessed	13		17		
CR	6	46.2%	6	35.3%	
PR	5	38.5%	10	58.8%	
SD	1	7.7%	Nil	0	
PD	1	7.7%	1	5.9%	
Overall RR = CR + PR	84.70%		94.10%		0.564
Radiological Response					
No. of patients assessed	14		16		
CR	6	42.9%	4	25%	
PR	7	50%	5	29.4%	
SD	1	7.1%	7	41.2%	
PD	Nil	0	Nil	0	
Overall RR = CR + PR	92.90%		54.40%		0.039

CR complete response, PR partial response, SD stable disease and PD progressive disease

The most common presenting clinical features in both groups were abdominal pain (68%), mass (42%) and ascites (42%). Pathological diagnosis was made by: cytology of ascitic fluid (54.8%), FNA of tumor mass (3.2%), image-guided core biopsy (38.8%) and open (surgical) biopsy (3.2%). All patients but one in each group received carboplatin and paclitaxel: one in group 1 developed hypersensitivity reaction to paclitaxel, so she was treated with single agent carboplatin while carboplatin and docetaxel was administered in one patient in group 2 due to the presence of pre-existing grade 1 peripheral neuropathy. In more than half the patients in both groups, six chemo cycles were administered

Table II : Safety of Chemotherapeutic Agents as measured by Adverse Effects

Adverse Effect	Group 1 Adjuvant Chemotherapy		Group 2 Neoadjuvant chemo		2-Tail : p-value
	No.	%	No.	%	
Hematologic toxicity, grade 3 and 4					
Neutropenia only	2	14.3	Nil	0	
Thrombocytopenia only	3	21.4	2	11.8	0.466
Both	1	7.1	9	52.9	
Nil	8	57.1	6	35.3	
Transfusions					
Packed RBCs†	2	14.3	5	39.4	
Platelets	Nil	0	Nil	0	0.411
Not required	12	85.7	12	64.6	
Febrile neutropenia					
Single episode	1	7.1	5	29.4	
More than one episode	Nil	0	1	5.9	0.094
Nil	13	92.9	11	64.7	

PRBCs packed red blood cells
Grades 1 and 2, and grades 3 and 4 according to revised National Cancer Institute's common toxicity criteria (NCI-CTC) version 2. [13]

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Biochemical and radiological Response Rates were assessed in 30 patients. One patient died during surgery precluding any response assessment. Specimens from 25 patients were reviewed for pathologic response. Disease remained irresectable in 2 patients in each group so they did not undergo surgery. One patient died with neutropenic sepsis after her last chemotherapy. Group 1 patients showed higher pathological (p = 0.039) and radiological responses (p = 0.001) and this translated to higher rates of OCRS after

ACT. Instead, patients from group 1 had better biochemical responses, (p = 0.564), (See table I).

Chemotoxicity profile is shown in table II. Patients after getting NACT had higher rates of hematological and non-hematologic toxicities and resulted in more blood transfusions, episodes for febrile neutropenia and delays in chemotherapy administration. One patient died from neutropenic sepsis in group 2.

Discussion

In this trial of the treatment of advanced OEC, we compared the results of NACT followed by surgery with ACT followed by interval cytoreductive surgery. ACT in patients with primary sub-optimal surgery resulted in better radiological and pathological results which translated into more patients undergoing undergoing OCRS. Larger tumor mass is characterized by poor blood supply to its center which results in necrosis and poor chemotherapy penetration.[15] In our opinion, upfront surgical resection (even if suboptimal) of some of the tumor in group 1 might have resulted in reduction of those poorly perfused areas, increasing penetration of ACT to most of the tumor mass and therefore leading to good response. Higher hematologic toxicity observed in group 2 patients could be the consequence of more women in that group having poor functional status and co-morbid conditions as shown by other studies.[16,17] It has resulted in delays in chemotherapy administration which is another factor for their relatively poor outcome. [18]

Another study showed radiological RR of 80% by RECIST criterion after NACT in 45 patients where 68.9% patients were able to undergo OCRS. All patients had microscopic residual disease.[7] An Indian study on NACT showed 52.2% radiological RR after NACT and the rate of OCRS was 45.6%.[19] In our study radiological RR after NACT was 54.4%, OCRS was performed in 76.4% and 11.2% of surgical specimens showed pathological CR. Despite having relatively poor radiological responses, more patients in our study had OCRS and achieved pathologic CR. In our view, we achieved better pathologic outcomes due to the use of more effective chemotherapy regimen (carboplatin and paclitaxel: given to 94% patients in our study and 77.8% patients[7] in another study with the same objective).

In the neoadjuvant chemotherapy group, biochemical response in the absence of radiological and pathological improvement is consistent with the findings of a meta-analysis of phase II trials showing that CA125 overestimates tumor response.[20] Failure of CA125 to accurately show tumor responses makes it role unclear in the pre-operative settings.[21] This unexpected biochemical effect is probably due to small sample size of neoadjuvant trials (including our study) which needs to be further evaluated.[22]

Major weaknesses of our studies were small sample size and the use of RR rather than survival analysis to assess the efficacy of treatment. Due to the non-specific symptoms at presentation, most patients with OEC undergo exploratory laparotomy and TAH/BSO before they are seen by Medical Oncologists. This makes it very difficult to obtain a large sample size for studying NACT.[23, 24] Due to the same reason, RR rather than survival was chosen as the study endpoint which is not the case in most chemotherapeutic trials.[25] Physicians need to be educated regarding upfront chemotherapy.[26, 27] NACT in OEC is a new concept in our country and due to the documented benefits of OCRS, most gynecologists attempt upfront surgery to give maximum benefits to their patients. We think that taking a step further, a large clinical trial determining survival benefit could be planned for future studies.

Conclusion

ACT is has more efficacy and safety for patients with ovarian epithelial cancer as compared to NACT. However our study is limited by small sample size and lack of survival data. Larger prospective studies are required to validate our results.

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