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Neoadjuvant Chemotherapy (NACT) In Advanced Epithelial Ovarian Cancer: A Review

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Abstract *— Ovarian cancer is considered to be the third most common cancer in Indian women and eight as global , 2018 facts sheet. It is a leading cause of death in Indian women due to cancer and fifth most common cause of death in women. The age that is affected by ovarian cancer is mostly above 50 years of women. Ovarian cancer is caused in ovaries and can also spread in the underlying organs if not diagnosed properly. Ovarian cancer can be divided further in two sub-types. Type1: Tumors mostly arise from the typical Borderline (proliferative) tumors. These are the early stage tumors [Stage I & II] Type2: Tumors are high-grade serious carcinomas, intraepithelial carcinoma and these are the advanced stage tumors having highly proliferative & rapid progression [Stage III & IV] This review mainly addresses the [Stage III & IV] diagnosis of Epithelial ovarian cancer by NACT (Neoadjuvant chemotherapy). The aim of this review is to evaluate the results and the possibilities of NACT procedure in curing Epithelial ovarian cancer.*

Keywords *— **EOC; cytoreduction; debulking surgeries; bevacizumab ;disparities in treatment; epithelial ovarian cancer; laparoscopy in oncology.***

I. INTRODUCTION

Ovarian cancer is a chemo-sensitive tumor and majority of the patients receive adjuvant chemotherapy. Recently, neoadjuvant chemotherapy (NACT) has been advocated for patients with advanced ovarian cancer with an aim to improve respectability rates and survival.

Neoadjuvant chemotherapy is a treatment for advanced ovarian cancer at [Stage III & IV]. Women undergoing NACT had significantly less blood loss than surgeries. These patients have shorter ICU & hospital stays and had improved progression- free survival . Neo-adjuvant chemotherapy (NACT) has been implemented mostly in treating advanced disease, with studies performed having numerous limitations. Data extrapolated from these studies have not shown inferiority survival of NACT, compared to primary debulking surgery. The role of NACT is of particular interest because of the intrinsic mechanisms that are involved in the process, which can be proven as therapeutic approaches with enormous potential. NACT increases immune infiltration and programmed death ligand-1 (PDL-1) expression, induces local immune activation, and can potentiate the immunogenicity of immune-exclude high grade serous ovarian tumors, while the combination of NACT with bevacizumab, PARP inhibitors or immunotherapy remains to be evaluated. This article summarizes all available data on studies implementing NACT in the treatment of ovarian cancer, focusing on clinical outcomes and study limitations.

High mortality rates observed among ovarian cancer patients necessitates the identification of more

effective treatments, along with biomarkers that will aidtreatment individualization.

II. ANALYSIS

Two retrospective analyses compared NACT and interval debulking to primary cytoreduction and adjuvant chemotherapy.

The first one comprised of twenty-one studies, including a total of 835 patients . This trial convincingly showed that the main parameters associated with patient survival were the use of platinum-based regimens and the performance of optimal debulking surgery. The above meta-analysis also reported that the weighted average median survival of patients subjected to NACT was 24.5 months.

Another meta-analysis of twenty-one studies showed that NACT indeed increased the rate of optimal cytoreduction, despite unfavorable conditions. This increase, however, did not have a favorable impact on improved OS, especially as compared with primary debulking surgery in patients with low-risk disease .

TRIALS :

The first trial implementing NACT in advanced ovarian cancer, the EORTC 55971 trial, randomized 632 patients to receive at least six cycles of platinum-based chemotherapy after primary cytoreductive surgery or three cycles of neoadjuvant platinum-based chemotherapy followed by interval debulking in patients with objective response or stable disease, followed by another three cycles of platinum- based chemotherapy. In the intention- to-treat population, median OS was similar inboth groups of patients (29 months in the primary surgery group vs. 30 months in the NACT group, HR=0.98, 90% confidence interval [CI], 0.84 to 1.13; p=0.01), as was progression-free survival (PFS), i.e., 12 months in both groups. The strongest independent predictive factors of improved OS were the absence of residual diseaseafter surgery, stage IIIC disease, small tumour size at randomization, endometrioid histology and younger age at diagnosis. the study included patients with extensive disease, a parameter that complicates the completion of R0 resection, the main independent prognostic factor in advanced ovarian cancer.

The Role of Bevacizumab :

The addition of bevacizumab to adjuvant chemotherapy followed by maintenance bevacizumab monotherapy after primary cytoreduction in stage IIIB-IV ovarian cancer has been associated with benefit in PFS, but had no significant impact on OS according to the initial analyses of two randomized phase III trials published in 2011 (GOG218 and ICON7) . randomized patients in a 2:1 to receive four 4 of NACT (paclitaxel 175mg/m2 and carboplatin 5 AUC, every three weeks) with or without bevacizumab . NACT with bevacizumab achieved high complete resection rate in patients who underwent IDS (85.5%). Although in patients with initially unresectable FIGO stage IIIC/IV ovarian, tubal, or peritoneal adenocarcinoma, the complete resection rate with the addition of bevacizumab was significantly higher than with chemotherapy alone, the role of bevacizumab in this setting should be further investigated. The results of two ongoing prospective trials are awaited. In conclusion, data show that the addition of bevacizumab to NACT is safe, however, its efficacy remains under evaluation.

The Role of PARP inhibitors :-

The use of PARP inhibitors (PARPi) has transformed the care of advanced high- grade serous/endometrioid ovarian cancer. Four phase III trials (SOLO-1, PAOLA- 1/ENGOT-OV25, PRIMA/ENGOT-OV26 and VELIA/GOG-3005) demonstrated remarkable improvements in progression-free survival with PARP inhibitor therapy (olaparib, niraparib or veliparib) for newly diagnosed ovarian cancer. PARP inhibitors play a pivotal role in the management of newly diagnosed ovarian cancer, which will affect subsequent treatment choices. Refinement of testing for patient selection and identification of regimens to treat populations that appear to benefit less from PARP inhibitors are a priority.

Other Combinations of drugs used in Epithelial ovarian cancer:

Chemotherapy for epithelial ovarian cancer is usually a combination of 2 or more drugs given every 3 to 4 weeks intravenously. Usually a platinum drug such as carboplatin or cisplatin is combined with a taxane drug such as paclitaxel or docetaxel. Combinations

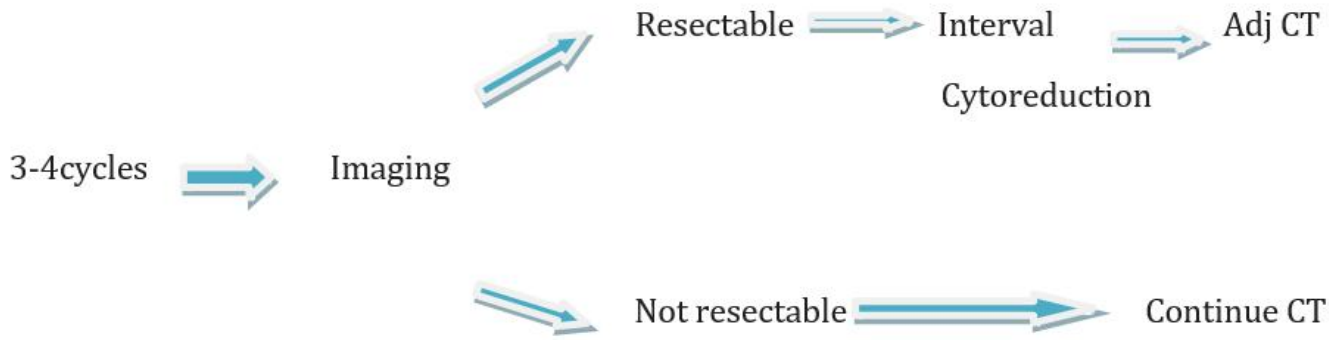
area :-

- carboplatin and paclitaxel
- carboplatin and docetaxel
- cisplatin and paclitaxel

IP chemotherapy is offered if having stage 3 epithelial ovarian cancer with tumourssmaller than 1 cm in size after primary surgical debulking. Cisplatin and paclitaxel are the drugs most often used in IP therapy.

III. STUDIES

For women who will undergo NACT , an initial 3cycles of IV carboplatin plus , paclitaxel with the addition of bevacizuman for those with high-risk disease iscarried out.



At Gujarat Cancer & Research Institute , Ahmedabad :

A hospital based studies were conducted at Gujarat Cancer & Research Institute , Ahmedabad during August 2008 - August 2010 for patients with advanced Epithelial Ovarian cancer .

A total of 50 patients were treated with NACT and followed up until August 2010 and response was analyzed.

All patients with stage IV disease and stage IIIC with large volume ascites (>500 ml), extensive peritoneal disease and CA125>500, not amenable for optimal cytoreduction and patients considered unresectable by the treating surgical team were subjected to NACT followed by surgical cytoreduction after obtaining an informed consent. Patients who had significant primary surgical cytoreduction (any cytoreductive procedure other than exploratory laparotomy and biopsy) elsewhere were excluded from the study. On presentation each patient was evaluated thoroughly by a detailed history regarding symptoms, past and family history. A thorough physical examination including Breast, neck, per abdomen, per speculum, per vaginal, per rectal examinations to assess ovarian mass, ascites, hepato- spleenomegaly, peritoneal disease, pleural effusion, supraclavicular lymph nodes, was performed. Radiological examination either USG pelvis or CT scan and Chest X- ray to evaluate the extent of disease, involvement and to decide staging and unresectability. Serum CA 125 level was measured in every patient on presentation and graded whether <500 or >500 to assess the response to NACT and for prognosis. Cytological or histopathological confirmation (USG guided biopsy from the ovarian mass) was done in each case before starting NACT.

The commonest combination used was cisplatin + cyclophosphamide (Arm A) or paclitaxel + carboplatin (Arm B) every 21 days. Each patient was monitored for chemotherapy related adverse reaction graded according to WHO criteria.

Response evaluation was done after 3rd/4th cycle of NACT and if there was no disease progression or tumor was responding, and if the disease was found clinically and radiologically resectable, patients were taken for interval cytoreductive surgery. Response of NACT was also assessed by extent of surgical resection possible (whether optimal or suboptimal debulking done).

After completion of postoperative adjuvant chemotherapy cycles, patients were followed up every 3 monthly by clinical and radiological examination and CA 125levels (if indicated) to detect local or systemic failure.

IV. RESULTS

Total 50 patients were included in the studies with advanced stage ovarian carcinoma who presented to the Institute between August 2008 and August2010.

Majority of patients 22(44%) were in age group of 40–50 years while only 3(6%) were among the 60–70 years. Mean age of patients was 50.14 ± 8.2 years. 78% patients were postmenopausal, 16% were premenopausal and 6% of the patients had surgical menopause. 90% of the patients were multiparous whereas 6% were nulliparous and 4% primiparous. Abdominal distension plus abdominal pain was the most common symptom amongst the 18(36%) patients followed by abdominal pain alone amongst 15(30%) of patients while only 4(8%) of the patients had bladder or bowel complaints along with abdominal distension.

Ascites was the commonest 37(74%) clinical finding while mass was palpable in 15(30%) and clinically palpable omental cake was found in 5(10%) patients whereas 6(12%) had no significant per abdomen findings. On per vaginal examination, forniceal fullness was found in 18(36%) of the patients while mass was palpable in 31(62%) of the patients and 1(2%) patient had no abnormal finding. Nodularity was found in pouch of doughlas on per rectal examination in36(72%) of the patients.

Pleural effusion was found in only 9(18%) while maximum 41(82%) of the patientshad normal chest X-ray. Maximum 37(74%) patients had CA 125 levels >500 on presentation followed by 13(26%) had CA 125 level 101–500 while none of the patients had baseline CA125 in the normal range. Range of baseline CA 125 was 164–5394.

31(62%) of the patients had pelvis as well as per abdomen disease on USG while 16(32%) had disease only in the pelvis and 3(6%) patients had only per abdomen disease that is ascites/liver/peritoneal metastasis with no evidence of pelvic masson USG.

Out of 26 patients with ascites, 21(81%) patients had positive ascitic fluid cytology for malignant cells while 5(55%) patients had pleural fluid cytology positive amongst 9 patients with pleural effusion.

There were 15 patients in Arm A and 35 patients in Arm B. Out of the total 50 patients, Majority 43(86%) patients had stage III disease while only 7(14%) were stage IV disease with 5 patients having positive pleural fluid cytology and 2 patients with liver metastasis. Mean number of neoadjuvant CT cycles given were 3 in both Arm A (66%) and in Arm B (71%).

After NACT 17(34%) patients had NED on USG while 27(54%) had disease confinedto pelvis only.

After surgery, 31(62%) patients had CR at the end of treatment and were evaluable with a median follow up of 19 months. 3 patients (6%) had gross residual disease at the end of treatment called the primary refractory disease. 1 patient died due to disease. 5 patients were lost to follow up. 2 patients (1 + 1 LFU) had recurrence with a median PFS of 3.5 months.

Study at Teritary Cancer Center :

These studies were done at a tertiary cancer center conducted b/w [2007-2017]. This was approved by the French ethical standards and 2008 Helsinki declaration [Ethical principles for medical research involving human subjects , including research on identifiable human material and data] .

All patients presenting confirmed newly diagnosed Stage IIIC & Stage IV HG-SOC were included in these studies. Patients underwent a complete workup , biologic workup , diagnostic laparoscopy .These patients went under biopsies that experts analyzed. All surgeries were performed by expert surgeons.

During the treatment course of the patients attributed to NACT , Four subcategories appeared based on the disease response to NACT. Patients not eligible for PDS due to disease extent underwent Paclitaxel-carboplatin-based NACT .Patients having Stage IV underwent systematic clinical ,biological and radiological evaluation of treatment at 3cycles .

Stage IV patients underwent surgery after 6 NACT cycles to ensure Treatment of extra- abdominal metastasis.

Stage III patients underwent NACT with an evaluation every three NACT cycles (CA125 levels , CT scan , and diagnostic laparoscopy).

Patients were categorized into two parts –based on the treatment strategy defined on the initial patients and disease characteristics during the tumor boards: PDS and NACT groups .

The NACT group was further divided into three sub –groups based on the number of cycles required before surgery :

- Early surgery <6 NACT cycles
- Surgery at 6 NACT cycles
- Delayed surgery >6 NACT cycles

Surgeries were classified into **Standard , radical , and supra – radical** .

Standard :- Hysterectomy, bilateral salpingo – oophorectomy, pelvic peritonectomy ,omentectomy , appendectomy, pelvicand para-aortic lymphadenectomy;

Radical :- Addition of recto-sigmoid resection

Supra-Radical :- Diaphragmatic peritonectomy , liver resection , spleenectomy , cholecystectomy and other digestive track resections.

Complete cytoreduction(CC0) was defined as the absence of any macroscopic residual disease at the end of surgery . postoperative residual disease was stratified according to the remaining disease after surgery and was CC1<0.25cm, CC2<2.25cm , CC3>2.5cm .

Surgery related complications were Evaluated during the hospital stay , at one and two months postoperatively. Follow-up visits were planned for one month aftetr surgery , then every four months for five years . During follow-up visits , patients underwent gynecological examination , CA125 level , and if needed , thoraco - abdominopelvic CTscan.

While estimating the association between survival and treatment modality (NACT versus PDS) using Cox models , an indication bias might occur as treatment choice might depend on initial characteristics . An ordinal logistic regression was used while analyzing treatment in three groups of surgery timing : <6 cycles of NACT , 6 cycles , >6 cycles. Thismodel was also performed to analyze the survival data when comparing the PDS and early NACT groups (<6 cycles).

Results :

The initial group included 254 patients , out of which 221 met the inclusion criteria. The median age of diagnosis was 63.2 years , with no difference between the groups . from these analysis it was concluded that patients , who underwent NACT presented significantly poorer Risk factors in comparison with other processes .

3-4 Cycles vs 6 Cycles NACT in Advanced Stage Epithelial OvarianCancer :

Out of 219 patients with advanced epithelial ovarian cancer,123 patients received 3-4 cycles and 96 patients received 6 cycles of platinum-based NACT. Afterwards, laparotomy was performed for interval cytoreductive surgery.

Results:

No statistically significant difference was found for DFS and OS of the patients who received 3-4 cycles and those who received 6 cycles of NACT (HR:1.047,95.0%CI [0.779- 1.407]; p:0.746 for DFS, and HR:1.181,95.0% CI [0.818-1.707]; p:0.368 for OS). Evaluating

123 patients who received 3-4 cycles of NACT;87 patients (70.7%) without macroscopic residual tumor after interval cytoreductive surgery had significantly longer DFS and OS compared to 36 patients(29.3%) with any residual tumor (HR:1.830,95.0% CI [1.194-2.806]; p:0.003 for DFS, and HR:1.946,95.0% CI [1.166-3.250]; p:0.009 for OS).96 patients

who received 6 courses of NACT were evaluated;63 patients (65.6%) without macroscopic residual tumor after interval cytoreductive surgery had significantly longer DFS and OS than 33 patients (34.4%) with any residual tumor (HR:1.716,95.0% CI [1.092-2.697];p:0.010 for DFS, and HR:1.921,95.0%CI [1.125-3.282]; p:0.013 for OS).

In patients with advanced ovarian cancer, there is no significant difference in DFS and OS between 3-4 cycles or 6 cycles of NACT.The most important factor determining survival iswhether macroscopic residual tumor tissue remains after interval cytoreductive surgery following NACT.

Use and outcomes of neoadjuvant chemotherapy (NACT) for treatment of less common epithelial ovarian cancer :

A retrospective cohort study and systematic literature analysis was conducted using the National Cancer Database from 2006 to 2017 and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program from 2006 to 2019. Data analysis was performed from July 2022 to April 2023. NACT use were assessed using multivariable analysis, and overall survival (OS) was assessed with the inverse probability of treatment weighting

propensity score.

This retrospective cohort study with a systematic review and meta-analysis examined data from the NCDB from 2006-2017 and SEER from 2006-2019. The starting point of 2006 was chosen because this was when data became available regarding the sequence of cancer-directed surgery and systemic chemotherapy in both databases. The study population included patients with stage III to IV ovarian cancer with clear cell, mucinous, and low-grade serous histologic subtypes .

Results:

Treatment with NACT was used in 253 patients (13.8%) with clear cell, 120 patients (10.4%) with low-grade serous, and 95 patients (10.6%) with mucinous carcinomasFrom 2006 to 2017, NACT use increased in clear cell carcinomas from 10.2% to 16.2% (58.8% relative increase; $P < .001$ for trend) and in low-grade serous carcinomas from 7.7% to 14.2% (84.4% relative increase; $P = .007$ for trend) . NACTuse also increased in mucinous carcinomas from 8.6% to 13.9% (61.6% relative increase; $P = .07$) .

Across the 3 histologic subtypes, older age and stage IV disease were independentlyassociated with NACT use. In a propensity score–weighted model, the NACT and PDS groups had comparable OS for clear cell (4-year rates, 31.4% vs 37.7%; hazard ratio [HR], 1.12; 95% CI, 0.95-1.33) and mucinous (27.0% vs 26.7%; HR, 0.90; 95%

CI, 0.68-1.19) carcinomas. For patients with low-grade serous carcinoma, NACT was associated with decreased OS compared with PDS (4-year rates, 56.4% vs 81.0%; HR, 2.12; 95% CI, 1.55-2.90). Increasing NACT use and histologic subtype–specific survival association were also found in the Surveillance, Epidemiology, and End Results Program cohort (n = 1447).

Treatment Evaluation :

- Before each NACT cycle, serial evaluations should be done
- Meantime history and physical examination
- Complete blood level count & checkups
- Liver and renal function tests
- CA 125 measurement
- Ct scan after three cycles of NACT
- Evaluation of the patient by Gynecologic and oncology surgeon

Side effects and risks :

Some of the possible side effects of chemotherapy includes :-

- nausea or vomiting
- hair loss
- nail or skin changes
- Loss of appetite & weight changes
- Diarrhea or constipation
- mouth sores
- fatigue
- higher rates of platinum resistance
- Elevated levels of aldehyde dehydrogenase 1 (ALDH1)
- Difficulty in detecting residual cancer cells during IDS
- Enhancement of stemness of ovarian cancer cells
- Induction of gene -mutation
- Treatment related toxicities increases
- Delay in the treatment
- It can be physically , socially , & Emotionally difficult for patients dealing with gynecologic malignancy unlike immediate removal.

Some Benefits of NACT procedures are :-

- This therapy reduces the risk of cancer coming back.
- This usually involves a treatmemt course of 3-4 months
- This therapy is adjustable according to the patients needs , circumstances and tolerance .
- shorter surgery time, less blood loss during surgery and shorter hospital admission

stay.

- It reduces preoperative morbidity and mortality.
- Increases complete resection of disease.
- It provides opportunity to monitor response during treatment and allows discontinuation of therapy in case of any difficulty & non-responsiveness.
- Improved long term survival.

V. CONCLUSION

The purpose of this review was to study the new technique of NACT chemotherapy in treating Epithelial Ovarian cancer . This concludes that NACT is an great therapy for reducing the mortality rate in women having ovarian cancer . This review states the studies which were being done in different areas of the world for the improved used of NACT in Ovarian Cancer. More advancement can be done in this field ijn order to Overcome the complications and Limitations of this theory.

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