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Response And Clinical Outcome of Locally Advanced Epithelial Ovarian Cancer to Neoadjuvant Chemotherapy with Paclitaxel and Carboplatin

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Abstract

This is a single institutional study of stage 3 and 4 epithelial ovarian cancer treated with neoadjuvant chemotherapy, paclitaxel and carboplatin during 2018- 2020 and underwent interval cytoreduction and was done to evaluate the pathological response in patients treated with neoadjuvant chemotherapy (NACT) for unresectable advanced-stage ovarian cancer. Response were classified into complete pathological response (cPR) and partial pathological response (pPR). Partial pathological response is again classified as microscopic residual and macroscopic residual disease with size <1cm or >1cm. Clinical outcome of the patient assessed as on January 2022 and classified as no evidence of disease(NED), relapsed treated and NED, relapsed treated and is having persistant disease, relapsed and progressed on palliative care, relapsed and progressed to death. Fifty-one patients (36 stage 3 and 15 stage 4) who fulfilled inclusion criteria after a median follow up of 22 months had Pathological complete response and partial response of13.7% and 86.3% respectively. Majority of patients relapsed and only 29.4% of patients were disease free and 17.6% of patients progressed to death. Clinical outcome is found to be better in patients with complete pathological response or microscopic residual disease or macroscopic residual disease < 1cm (p value- 0.00092). Complete pathological response of advanced carcinoma ovary is rare. Patients with complete pathological response or microscopic residual disease or macroscopic residual disease of size <1cm after NACT has less incidence of relapse.

Keywords: Ovarian Cancer, Neoadjuvant Chemotherapy, Pathological Response

Introduction

sOvarian cancer is the fourth most common cancer in Indian women. Age standardised incidence rate of the same is 6.6 cases per 100000 (GLOBOCON 2020).[(1)]Epithelial ovarian carcinoma is the most common type ovarian cancer which includes high grade serous carcinoma (70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%), low grade serous carcinoma (<5%).[(2)] Germ cell

tumours account for 5% of ovarian cancers and sex cord stromal tumours account for 7% of ovarian cancers.[3] All these cancers vary in their prognosis based on the difference in their molecular profile, clinical presentation, pattern of spread and response to chemotherapy. 70% of epithelial ovarian carcinoma presents in stage 3 or 4. Delay in diagnosis occurs due to non specific symptoms in patients and absence of effective screening modalities. Management of carcinoma ovary depends on the stage of the disease. Surgery is the primary modality of management in carcinoma ovary. In stage 1A and 1B tumours fertility sparing surgical approaches can also be considered. Complete resection during cytoreductive surgery is the most important independent prognostic factor in advanced epithelial ovarian cancer. Neoadjuvant chemotherapy(NACT) is a treatment approach that is getting popularity as an alternative to primary cytoreductive surgery for management of advanced epithelial ovarian cancer. Several studies suggest that neoadjuvant chemotherapy offers better optimal debulking with less surgical morbidity in females with ovarian carcinoma compared with primary cytoreductive surgery.[4,5]

The treatment of surgically unresectable epithelial carcinomas of ovary with neoadjuvant chemotherapy using paclitaxel and carboplatin is popularized world wide recently. This is an effort to analyse the response to the above mentioned treatment conducted in an Indian setup as a single institutional study done at a Government Medical College in Kerala.

Patients and methods

This is a single arm retrospective observational study done in the Department of Radiation oncology, Government Medical College, Thrissur, Kerala, India.

Patients who attended the Radiotherapy OPD of Government Medical College, Thrissur with histologically proven, previously untreated, carcinoma of ovary during 2018 - 2020 with inclusion criteria:

1 Tumours of clinical stage 3 - 4
2 Surgically inoperable, loco regionally advanced disease
3 Age between 18 and 70 years
4 Perfomance score of 0- 2
5 WBC count greater than 4000 cells/ml
6 An absolute neutrophil count greater than 37.5%
7 Platelet count more than 1 lakh cells/ml
8 Serum creatinine < 1.5mg/dl
9 Creatinine clearance >80ml/min
10 Hemoglobin value > 8gm%
11 Received neoadjuvant chemotherapy with paclitaxel (175mg/m2)and carboplatin (5AUC) 3 weekly cycle

Were selected to apply the exclusion criteria:

1 Operable carcinoma of ovary
2 History of coronary artery disease, renal disease, uncontrolled hypertension.
3 Previous history of any carcinoma and irradiation

Datas of the patients fulfilling the above criterias including age, performance score, stage of the disease, initial imaging modality, number of chemotherapy cycles are recorded from the medical records library All operable patients after neoadjuvant chemotherapy who were send for cytoreductive surgery are selected from the cohort and response to chemotherapy is assessed with postoperative histopathology report and is classified as partial pathological response and complete pathological response depending on the residual disease. Patients who drop out or do not complete planned course of treatment are excluded. Patients are clinically assessed as on January 2022 and response is assessed as follow up with no evidence of disease (NED), relapsed treated and NED, relapsed treated and is having persistent disease, relapsed and progressed on palliative care and relapsed and progressed to death

Results

51 patients treated between 2018- 2020 was selected. 36 patients had stage 3 disease (70.6%) and 15 patients had stage 4 disease (29.4%). Patient characteristics are detailed in Table 1. Median age of patients was 55 years (range, 36- 75 years).

7 patients underwent ultrasound (USG) abdomen as initial imaging modality whereas 37 patients underwent contrast enhanced computed tomography (CECT) abdomen and pelvis and 6 patients underwent magnetic resonance imaging (MRI) pelvis. Only 6 patients underwent positron emission tomography (PET).

All underwent chemotherapy with paclitaxel and carboplatin chemotherapy. Number of chemotherapy cycles varied ranging from 3- 8 cycles. 4 patients received less than 4 cycles of chemotherapy whereas 41 patients received 4- 6 cycles of chemotherapy and only 6 patients received more than 6 cycles of chemotherapy.

General characteristics of patients- Table 1

	NO. of patients
Age	
</=40 years	5 (9.8%)
41- 50 years	10 (19.6%)
51- 60 years	16 (31.4%)
>/61 years	20 (39.2%)
Stage	
3	36 (70.6%)
4	15 (29.4%)
Imaging modality	
USG	7(13.7%)
CECT	37(72.5%)
MRI	6 (11.8%)
PET	1(2%)
Number of chemotherapy	
<4	4 (7.8%)
4- 6	41 (80.4%)
>6	6 (11.8%)

All patients underwent interval cytoreduction after completion of chemotherapy and reevaluation with imaging. Histopathological report was studied and the pathological response to chemotherapy was classified as complete pathological response which was seen in 7 patients (13.72%) and partial pathological response seen in 44 patients (86.27%)

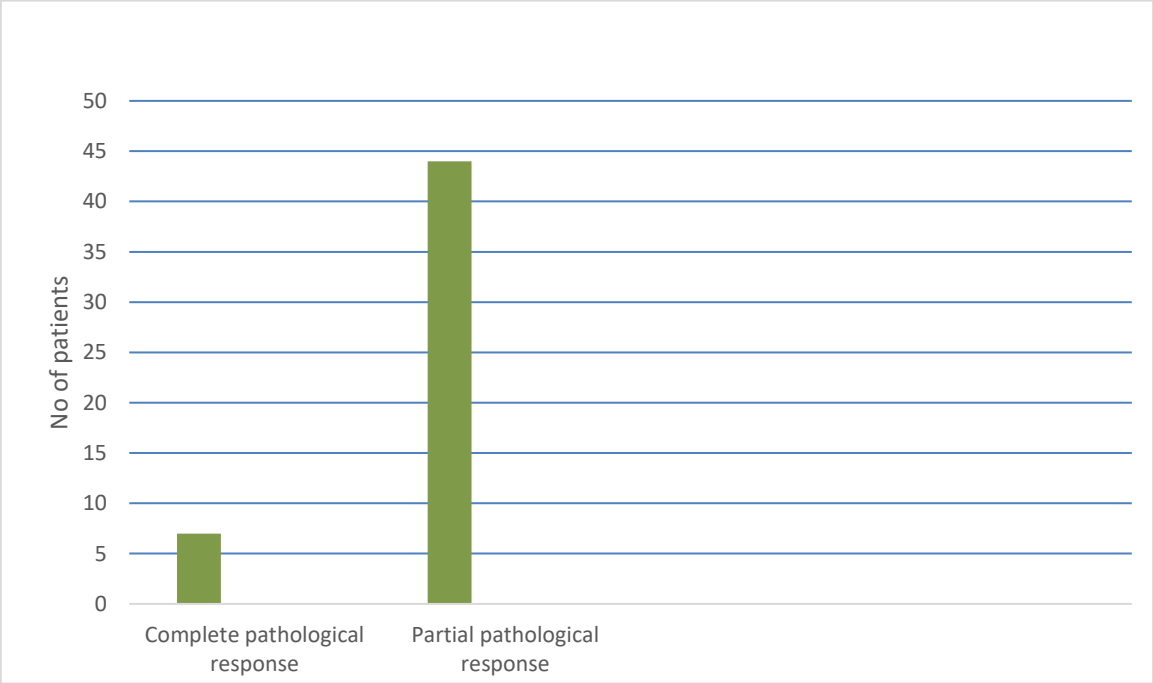

Figure 1- pathological response

Partial pathological response was then classified as microscopic and macroscopic residual tumour. Out of 44 patients with partial response, 7 patients had microscopic partial response (15.9%) and 37 patients had macroscopic partial response (84.1%).
The size of the residual tumour in macroscopic disease was assessed and it was noted that 3 patients only had a residual tumour of size <1cm (6.82%) and 31 patients had tumour size >1cm (70.45%)- Table 2

Residual disease- Table 2

Residual disease	No of patients
Microscopic disease	7 (15.9%)
Macroscopic disease < 1cm	3(6.82%)
Macroscopic disease > 1cm	34(77.27%)

After a median follow up of 22 months (5- 42 months) patients were reassessed on January 2022 and were identified to have NED in 15 patients (29.4%), relapsed treated and NED only in 1 patient (1.96%), relapsed treated and is having persistent disease in 16 patients (31.37%), relapsed and progressed on palliative care in 10 patients (19.6%) and relapsed and progressed to death were 9 patients (17.65%)- Table 3

Clinical outcome- Table 3

Clinical outcome	No of patients
NED	15 (29.4%)
Relapsed, treated and NED	1 (2%)
Relapsed, treated with persistent disease	(31.4%)
Relapsed and progressed on palliative care	10 (19.6%)
Relapsed and progressed to death	9 (17.6%)

So while comparing the response with the outcome by combining the above two associations we can see that 15 patients has attained a complete pathological response or microscopic pathological response or macroscopic residual tumour <1cm to the neoadjuvant chemotherapy. In these 15 patients 11 patients have clinically NED at the time of reevaluation (p- 0.00092)

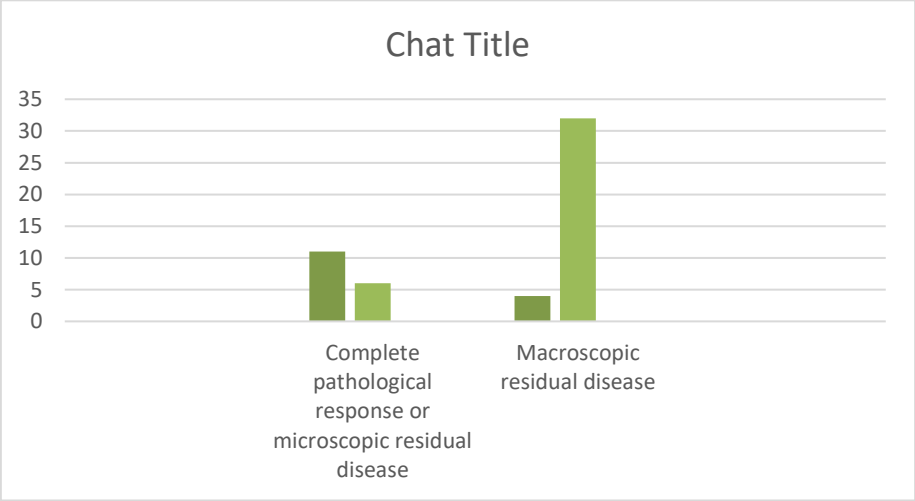

Figure 2- Complete pathological response and microscopic disease vs macroscopic disease

Discussion

The main treatment modality of stage 1 to 4 epithelial ovarian carcinoma is surgery. Complete resection during the cytoreductive surgery is one of the prognostic factor in advanced epithelial ovarian carcinoma. Survival is found to have an inverse relationship with the residual disease after the surgery. In a meta analysis of stage 3 and 4 epithelial ovarian cancer which included 6885 patients found that 5.5% increase in median survival rates were seen with every 10% increase in the maximal cytoreduction rates.(6)

Another review of 11999 patients with advanced carcinoma of ovary found that median overall survival was 70 months in patients who had no residual disease compared with 53 months in patient s with 1-5mm residual lesion, 40 months in patients with 1-10mm residual lesion and 30 months in patients with >10mm residual lesion.(7) So the aim of the cytoreductive surgery should be to achieve a complete resection with no residual disease.

Patients with advanced stage carcinoma ovary rarely achieves optimal debulking by primary cytoreductive surgery. So NACT before cytoreductive surgery was extensively studied in carcinoma ovary aiming at improving the debulking and thereby improving the survival of the patient. But EORTC and MRC trials has shown no benefit in the progression free survival(PFS) and overall survival(OS) between patients who underwent primary cytoreductive surgery and who underwent NACT followed by cytoreduction. (8,9)

The optimal duration for NACT is not defined in the literature. Platinum agents are the most active class of compounds in the adjuvant treatment of ovarian cancer. Before 1980s alkylating based regimens including cyclophosphamide and doxorubicin were used with a clinical response rates of 15- 20%. GOG 47 demonstrated an improvement in the clinical complete response rates(51% vs 26%) and PFS (13 vs 8 months) with addition of cisplatin with cyclophosphamide and doxorubicin.(10) since then cisplatin was used extensively in both single agent and multi agent drug trials.

GOG 111 compared cisplatin and paclitaxel vs cisplatin and cyclophosphamide in womens with suboptimally debulked large ovarian carcinomas and found thatimproved clinical response rates (73% vs 60%) and PFS (18 vs 13 months) and OS (38 vs 24 months) was seen in patients with paclitaxel containing arm.(11) Similarly a non inferiority trial of GOG compared paclitaxel cisplatin with paclitaxel and carboplatin with comparable median PFS and OS.(12) Hence paclitaxel and carboplatin based chemotherapy is more preferred as the regimen in NACT for advanced ovarian carcinoma.

Only few studies are there which evaluates the pathological response of ovarian cancer to the NACT. According to the studies pathological complete response is rarely observed in carcinoma ovary and ranges from 0- 14% and is demonstrated to have improved clinical outcomes. (13,14,15,16,17,18)

Till date no histopathological criteria has been established to describe treatment response after neoadjuvant chemotherapy. Residual tumour size after neoadjuvant chemotherapy was the only criterion significantly correlated with treatment response and subsequent overall survival. Studies has shown an overall survival of 45.6 months with NACT in advanced ovarian carcinoma.(13)

In a small retrospective study done in 16 patients with advanced epithelial ovarian cancer a complete pathological response of 12.5% and a partial pathological response of 50% is noted.(14)

Retrospective study done in 58 patients who evaluated the pathological response and event free survival has shown that 13.79% patients has attained complete pathological response but the degree of histological response has a limited impact on the survival when complete debulking surgery is achieved at interval cytoreduction.(15)

A retrospective study done by Petrillo et al in 322 patients assessed the pathological response after NACT as complete pathological response, microscopic and macroscopic residual disease. cPR is an uncommon event in patients receiving NACT and is associated with a longer progression-free survival and overall survival compared with women showing no cPR, even in patients receiving IDS with no gross residual disease. And the proposed classification of pathological response is expected to serve as an easily assessable and highly valuable prognostic tool in this clinical setting in the future. This was the classification that we considered in our study too.

No data evaluated relationship between the clinical outcome and the pathological response so far. Newer neoadjuvant regimens including PDL1 inhibitors are tried in the treatment of carcinoma ovary and the possibility of a personalised treatment with the help of molecular markers are under trial[19]

Conclusion

In our study, pathological complete response was noted in 13.7% of patients similar to the data available till date showing that complete response with NACT is a rare observation. In patients who completed NACT and cytoreductive surgery, the incidence of disease relapse is very high and majority of such patients are managed with second or third line chemotherapy. There is good clinical response with decreased incidence of relapse for patients with complete pathological disease, microscopic residual disease or macroscopic residual disease <1cm after NACT than those with macroscopic residual disease >1cm after NACT, who relapsed after the treatment. This is a potential area of research.

Limitations

Our data is single institutional retrospective data with small sample size. Hence prospective studies with large sample size is recommended for the confirmation of the result

Conflict of Interest

Nil

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Statements and declarations

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Reference

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021: 71: 209-249.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74
3. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol 2006;20:207.

4. Vergote I, Trope´ CG, Amant F: Neoadjuvant chemotherapy or primary surgery in Stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943–953.
5. Kang S, Nam BH: Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer?
6. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol 2002;20:1248-59
7. Chiva LM, Castellanos T, Alonso S, Gonzalez-Martin A. Minimal macroscopic residual disease (0.1-1 cm). Is it still a surgical goal in advanced ovarian cancer? Int J Gynecol Cancer 2016;26:906-11.
8. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53
9. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386:249-57.
10. Omura GA, Bundy BN, Berek JS, Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a GOG study. J Clin Oncol. 1989;7:457–465.
11. McGuire WP, III, Hoskins WJ, Brady MF. A Phase III randomized study of cyclophosphamide and cisplatin versus paclitaxel and cisplatin in patients with suboptimal stage III and IV epithelial ovarian cancer. N Engl J Med. 1996;334:1–6.
12. Ozols R, Bundy BN, Greer BE. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a GOG study. J Clin Oncol. 2003;21:3194–3200.
13. Sassen S, Schmalfeldt B, Avril N. Histopathologic assessment of tumor regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer. Hum Pathol 2007;38:926-34.
14. Miller K, Price JH, Dobbs SP. An immunohistochemical and morphological analysis of post-chemotherapy ovarian carcinoma. J Clin Pathol 2008;61:652-7.
15. Ferron JG, Uzan C, Rey A. Histological response is not a prognostic factor after neoadjuvant chemotherapy in advanced-stage ovarian cancer with no residual disease. Eur J Obstet Gynecol Reprod Biol 2009;147:101-5.
16. Muraji M, Sudo T, Iwasaki S. Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and debulking surgery. Gynecol Oncol 2013;131:531-4.
17. Petrillo M, Zannoni GF, Tortorella L. Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer. Am J Obstet Gynecol 2014;211:632.e1-8
18. Gorodnova TV, Kotiv KB, Ivantsov AO. Efficacy of Neoadjuvant Therapy with Cisplatin Plus Mitomycin C in BRCA1-Mutated Ovarian Cancer. Int J Gynecol Cancer 2018;28:1498-506
19. Nikolaidi A, Fountzilas E, Fostira F, Psyrri A, Gogas H and Papadimitriou C (2022) Neoadjuvant treatment in ovarian cancer: New perspectives, new challenges. Front. Oncol. 12:820128. doi: 10.3389/fonc.2022.820128