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RETROSPECTIVE ANALYSIS OF CHEMOTHERAPY IN PLATINUM SENSITIVE RECURRENT OVARIAN CANCER

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ABSTRACT **Purpose:** The aim of this study is to analyse the outcomes of platinum-sensitive recurrent ovarian cancer treated with Gemcitabine and carboplatin (GC) versus Paclitaxel and carboplatin (CP).

Materials And Methods: This is a single institutional retrospective study done by analysing the medical records of patients with platinum sensitive recurrent epithelial ovarian cancer. Two regimens were analysed, paclitaxel-carboplatin and gemcitabine-carboplatin. Outcomes analysed were PFS and OS.

Results: 124 patients with recurrent platinum sensitive ovarian cancer who received GC or CP chemotherapy were analysed. Demographic and clinical characteristics were comparable between groups. The period between the final platinum treatment and relapse ranged from 6.2 to 75.4 months with medians of 13.6 and 14 months, respectively. The side effects were tolerable and more than 85% of the patients in each group received more than 6 cycles of chemotherapy. The response rate and disease control rate were 67%, 81% in GC group and 74%, 85% in CP groups. Median PFS was 9.6 months in the GC group and 10.9 months in the CP group. Median OS was 34.6 months in the CP group and 36.7 months in the CP group

Conclusion: PFS and OS between the groups were not significantly different. Despite of hematologic toxicity profile of gemcitabine combination, judicious use of GCSF with gemcitabine regimens would help to avoid toxicity related delays and discontinuation of chemotherapy. Gemcitabine –carboplatin combination can be used as an equally effective alternative to carboplatin-paclitaxel in platinum sensitive recurrent ovarian cancer.

KEYWORDS : Platinum-sensitive, Recurrent ovarian cancer, Gemcitabine

INTRODUCTION:

Epithelial Ovarian cancer is an intractable disease with repeated recurrences and has the worst prognosis among all gynaecologic cancers.[1] Worldwide more than 238,000 new cases are diagnosed every year.[2] Although most patients with advanced stages of ovarian cancer respond well to initial cytoreductive surgery followed by standard combination of paclitaxel and carboplatin as adjuvant chemotherapy, recurrence of the disease is frequent. Approximately 23% of patients relapse during or within 6 months after end of primary chemotherapy and 60% relapse after 6 months.[3] The standard approach for treating recurrent ovarian cancer is chemotherapy and the option of secondary cytoreduction applicable only in highly selected group.[3] Most patients undergo four to five cycles of chemotherapy and deciding the drugs for treating the recurrence is a perplexing issue. Platinum sensitivity, residual toxicity, age, performance status, treatment free interval, and the impact on quality of life due to the adverse effects of treatment should be considered.[4]

Second line chemotherapy may include a combination regimen or single-agent regimens showing some benefit for treatment of recurrent ovarian cancer including: carboplatin, paclitaxel, pegylated liposomal doxorubicin, gemcitabine, bevacizumab, or more recently one of the new PARP inhibitors. For decades, taxane with platinum-based regimens has a major role in platinum-sensitive (PS) recurrent ovarian cancer. The unexpected neurotoxicity with the re-induction carboplatin-paclitaxel regimen showed the need to choose a platinum combination more carefully and studies suggested that gemcitabine with carboplatin might be a potentially useful combination with significant efficacy in recurrent settings as does the platinum based combination with PLD. Furthermore, the non-hematologic toxicity profiles of both agents, including neurotoxicity, do not overlap.

Gemcitabine is a nucleoside analog which exerts its chemotherapeutic activity by incorporation into DNA causing apoptosis. Myelosuppression was the most commonly reported toxicity with gemcitabine.[5] Other reported toxicities include hematologic toxicity, flu-like symptoms, nausea, vomiting, and appetite suppression . Based on a previous randomized study by Pfisterer and colleagues, carboplatin in combination with gemcitabine demonstrates greater efficacy through improved overall response rate (ORR) and median progression free survival in comparison to carboplatin alone.[7] Our study aimed at comparing the outcomes of combined regimens paclitaxel-carboplatin and gemcitabine carboplatin in second line settings

MATERIALS AND METHOD

This is a single institutional retrospective study. The medical records of patients with PS recurrent epithelial ovarian cancer from 2014 to 2017 were analysed after being approved by the departmental review board of the institution. Patients were considered eligible if recurrence occurred more than 6 months from previous platinum-based treatment and received paclitaxel-carboplatin or gemcitabine carboplatin during the relapse.

Two regimens were analysed in this study - Paclitaxel-carboplatin and Gemcitabine-carboplatin. Dosage used in CP regimen was paclitaxel 175mg/m2 with carboplatin (AUC-6) every 3 weeks. In GC regimen gemcitabine 1000mg/m2 (D1 & D8) with carboplatin (AUC-5) every 3 weeks was used. Prophylactic G-CSF was used whenever appropriate. RECIST and GCIG CA-125 criteria were used for evaluation of tumour response. Outcomes analysed were Progression free survival (PFS) and overall survival (OS).

The statistical analysis was performed using SPSS, version 24. Kaplan-Meier curves and Cox–regression analysis were used for analysis of survival data. P-value <0.05 was considered statistically significant.

RESULTS

In total, 124 patients with recurrent platinum sensitive ovarian cancer who received GC or CP chemotherapy in our hospital were analysed. Demographic and clinical characteristics are shown in Table 1. The mean ages of the patients were 54 and 56 years, respectively. Majority of the patients were diagnosed at an advanced stage (stage III or IV, 80% in the GC group and 82% in the CP group) with histologically confirmed serous carcinoma (81% in the GC group and 78% in the CP group). Patients with an early stage higher than IC were treated with CP as adjuvant chemotherapy after the primary surgery.

Table-1. Characteristics Of The Population.

CHARACTERISTICS	GC	CP	p-value
Number of patients	61	63	
Mean Age (years)	54	56	0.1123
Optimal Cytoreduction	45 (73%)	47 (74%)	
Suboptimal Cytoreduction	16 (26%)	16 (26%)	
Initial FIGO STAGE:			0.0599
I - II	12 (19%)	11 (17%)	
III - IV	49 (80%)	52 (82%)	
Primary Histology			0.3346

Serous	50 (81%)	49 (78%)	
Endometroid	5 (8%)	6 (9%)	
Clear cell	3 (4%)	3 (4%)	
Mucinous	3 (4%)	5 (7%)	
others	0	0	
Platinum Free Interval			0.7886
Median	13.6 months	14 months	
Range	6.2- 76.2	6.2 – 75.1	
6-12 months	27 (44%)	30 (47%)	
> 12 months	34 (55%)	33 (52%)	
No. of patients with grade 3/4 toxicity	2	1	
G-CSF	38%	12%	0.0017
No. of patients completed 6 cycles	53 (86%)	54 (85%)	
Chemotherapy response			0.1367
Complete response	28 (45%)	33 (52%)	
Partial response	12 (19%)	16 (25%)	
Stable disease	4 (6%)	7 (11%)	
Progressive disease	7 (11%)	8 (12%)	
*FIGO-International Federation of Gynaecology and Obstetrics, *RD- Residual disease. *G- Grade			

The period between the final platinum treatment and relapse ranged from 6.2 to 75.4 months with medians of 13.6 and 14 months, respectively. Similarly, in both groups, the disease recurred within 6 to 12 months in 44% of the patients, 51% of them recurred after 12months. Detailed toxicities of chemotherapy were not reported in this study; however, the side effects were tolerable and more than 85% of the patients in each group received more than 6 cycles of chemotherapy. Cessation of chemotherapy was mainly due to disease progression and due to toxicity in 2 patients in GC group and 1 patient in CP group.

Table-2 : Results Of Study			
RESULTS	**GC**	**CP**	**P-VALUE**
Median PFS	9.6 months	10.9 months	0.571
Median OS	34.6 months	36.7 months	0.760
*PFS- Progression Free Survival, *OS-Overall Survival *GC-Gemcitabine-Carboplatin *CP-Carboplatin-Paclitaxel			

Evaluation with CA-125 levels and CT scan was done and found that the response rate and disease control rate were 67%, 81% in GC group and 74%, 85% in CP groups. Median PFS was 9.6 months in the GC group and 10.9 months in the CP group (Figure 1). Median OS was 34.6 months in the CP group and 36.7 months in the CP group. Patients were further stratified for subgroup analysis according to platinum-free interval (PFI) and times of recurrence. The results revealed that median PFS was not statistically different in the groups.

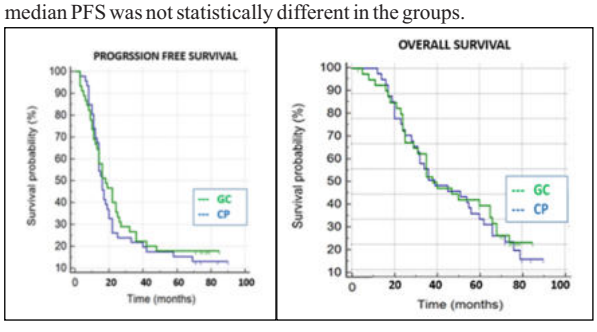

Figure 1 Kaplan-Meier analysis of PFS and 0S

DISCUSSION:

With the propensity of repeated recurrences, consideration into quality of life is an essential factor in decision-making about chemotherapy regimens in recurrent ovarian cancer. Despite the effectiveness of paclitaxel in ovarian cancer survival, its major side effects of hair loss and neuropathy are distressing for most patients.[7] In our study, we compared the outcomes of combined regimens paclitaxel-carboplatin and gemcitabine carboplatin in second line settings. The combination of Gemcitabine-carboplatin with and without bevacizumab was studied in OCEANS trial.[8]

In our study, the PFS and OS were 9.6 and 34.6 months for GC group which is comparable with the results of OCEANS trial. In comparison to the OCEANS trial in which more percentage of patients received cytoreductive surgery for the recurrence, our study did not have secondary cytoreductive surgery data.

Recent advances in the molecular basis of ovarian cancer cells, including intra-tumoral and inter-tumoral heterogeneity gives a better understanding of the mechanisms for tumour recurrence and therapeutic resistance.[9] Cancer stem cells have different characteristics by which they survive from therapies eliminating fast dividing tumour cells.[10] Growth from the stem cells slowly develops recurrent tumours which may be genetically distinct from previous tumours, thus causing multiple recurrences and metastases.

The molecular basis that predicts the chemo-sensitivity of recurrent ovarian cancer has been investigated in past decade in many studies. Assessment of tumour subtype-specific mutations and molecular aberrations indicated distinct clinical behaviours in recurrent ovarian cancer.[11] Most notably, regardless of platinum sensitivity patients with BRCA mutations exhibited delayed relapse and improved prognosis.[12] Determining the chemo-sensitivity of recurrence in ovarian cancer has became even more complex after restored protein function being reported after treatment for cancer related to secondary BRCA mutation.[13]

Recent treatment of ovarian cancer had even gone beyond combination chemotherapy. Breakthrough drugs as PARP inhibitors,[14] anti-angiogenesis bevacizumab[15] and immunotherapy[16] had yielded promising results in the recent trials. Therefore, current efforts need focus on optimizing the use of chemotherapy with multiple alternative strategies after carefully evaluated and used appropriately in the treatment of ovarian cancer.

The retrospective nature of the study with small sample size is a limitation of our study. Patients were been treated with GC or CP according to the physicians' preference which may cause selection bias. Moreover, toxicity profiles were not precisely documented in the medical records and could not be analysed in our study. Inclusion of consecutive cases from multiple institutes is necessary to confirm our results.

CONCLUSION:

Real-world experience of comparable outcomes in recurrent PS ovarian cancer treated with GC versus CP was presented in this study. PFS and OS between the groups were not significantly different. Despite of hematologic toxicity profile of gemcitabine combination, judicious use of GCSF with gemcitabine regimens would help to avoid toxicity related delays and discontinuation of chemotherapy. Gemcitabine –carboplatin combination can be used as an equally effective alternative to carboplatin-paclitaxel in platinum sensitive recurrent ovarian cancer.

DECLARATIONS

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REFERENCES:

1. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Women's Health. 2019;11:287–299. doi:10.2147/IJWH.S197604
2. Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer. 2017;140(11): 2451–2460. doi:10.1002/ijc.v140.11
3. A. du Bois, A. Reuss, E. Pujade-Lauraine, et al.Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO) Cancer, 115 (2009), pp. 1234-1244.
4. Bergamini A, Bocciolone L, Fodor A, Candiani M, Mangili G. Management of recurrent ovarian cancer: when platinum-based regimens are not a therapeutic option. *Int J Gynecologic Cancer*. 2019;ijgc-2019-000624.
5. Thigpen T. The role of gemcitabine in first-line treatment of advanced ovarian carcinoma. Semin Oncol. 2006;33:S26–32
6. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006;24:4699–707
7. Ozols RF, Bundy BN, Greer BE, et al. 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;21:3194–200.
8. C. Aghajanian, B. Goff, L.R. Nycum, et al.Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer Gynecol Oncol, 139 (2015), pp. 10-16
9. Jiménez-Sánchez A, Memon D, Pourpe S, et al. Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient. *Cell*. 2017;170(5):927–938.e920. doi:10.1016/j.cell.2017.07.025
10. Roberts CM, Cardenas C, Tedja R. The role of intra-tumoral heterogeneity and its clinical relevance in epithelial ovarian cancer recurrence and metastasis. *Cancers*. 019;11(8):1083. doi:10.3390/cancers11081083
11. Hollis RL, Gourley C, L Hollis R. Genetic and molecular changes in ovarian cancer.

Cancer Biol Med. 2016;13(2):236–247. doi:10.20892/j.issn.2095-3941.2016.0024
12. Safra T, Borgato L, Nicoletto MO, et al. Grenader TJMct: BRCA mutation status and determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin.2011;10(10):2000–2007. doi:10.1158/1535-7163.MCT-11-0272
13. Mayor P, Gay LM, Lele S, Elvin JA. BRCA1 reversion mutation acquired after treatment identified by liquid biopsy. *Gynecologic Oncol Rep*. 2017;21:57–60. doi:10.1016/j.gore.2017.06.010
14. Markman M. Pharmaceutical management of ovarian cancer: current status. *Drugs*. 2019;79(11):1231–1239. doi:10.1007/s40265-019-01158-1.
15. Shoji T, Eto H, Sato T, et al. A new therapeutic strategy for recurrent ovarian cancer – bevacizumab beyond progressive disease. *Healthcare*. 2019;7:3. doi:10.3390/healthcare7030109