Acta Pharm. **69** (2019) 87–97 Original research paper

https://doi.org/10.2478/acph-2019-0002

Comparison of clinico-pathological characteristics and survival of recurrent ovarian cancer patients on seven different chemo-protocols

SAIMA SATTAR[1]
MOBASHER AHMAD[1]
HAMID SAEED[1*]
ZIKRIA SALEEM[1]
ZEESHAN DANISH[1]
MUHAMMAD AKHLAQ[2]

[1] *Section of Clinical Pharmacy*
University College of Pharmacy
University of the Punjab
Allama Iqbal Campus
54000, Lahore, Pakistan

[2] *Department of Pharmaceutics*
Faculty of Pharmacy
Gomal University
Dera Ismail Khan
Khyber Pakhtunkhwa, Pakistan

Despite growing prevalence of ovarian cancer (OC) in Pakistan, no literature evidence exists regarding its clinic--pathological characteristics, survival and compliance of patients with recurrent ovarian cancer on various chemo--protocols. An observational study was conducted by enrolling 251 recurrent OC patients on 7 different chemo--protocols, from a specialized cancer care hospital, Lahore, Pakistan, using convenient judgmental sampling. The study was conducted for a period of 6 months. Most of the patients were between 18 and 70 years of age, with IIIC FIGO stage and papillary serous histological grade. As per RECIST, improved partial response (PR) (63.3 %) and complete response (CR) (52.1 %) was observed in the CP (carboplatin + paclitaxel) arm, substantiated by improved median progression free survival (PFS) and overall survival (OS) in CP and CD (carboplatin + docetaxel) arms, respectively, yet with no significant differences in survival curves, PFS (p = 0.12) and OS (p = 0.22). Interestingly, the highest and the lowest patient non-compliance were observed in CG (carboplatin + gemcitabine) (81.6 %) and paclitaxel (4.5 %) arms, resp. As per the hazard model for survival, topotecan showed significant association with the therapy related events/deaths compared to other protocols. These data suggest that CP regimen exhibited improved clinical efficacy and decreased toxicity related non-compliance in recurrent ovarian cancer patients of Lahore.

Keywords: ovarian cancer, carboplatin plus paclitaxel, topotecan, bevacizumab, docetaxel

Accepted July 16, 2018
Published online August 10, 2018

In women, ovarian cancer (OC) is the fourth most common cause of death and sixth most common type of cancer – making it a leading cause of mortality from all gynecological malignancies (1, 2). In the majority of cases, ovarian cancer, rare before the age of

* Correspondence; e-mail: hamid.pharmacy@pu.edu.pk

40, is predominantly diagnosed in elderly postmenopausal women above 50 years of age (3). In routine clinical practice, OC diagnosis is made incidentally during the work-up of another clinical condition, while symptoms remain poorly defined with no definite indices to screen the asymptomatic women; however, if confined to ovaries, it is highly curable with improved five-year survival (4). Most patients are referred to the clinics with an advanced stage of disease – FIGO (International Federation of Gynecological Oncology) stage III and IV, requiring aggressive surgery and chemotherapy (5).

Over the last several years, carboplatin plus platinum based regimen has been the standard first line chemotherapy in ovarian cancer. However, despite 60–80 % response rate with carboplatin and paclitaxel, the majority of patients subsequently relapse and need further clinical management (3, 6). In this context, in previous years, numerous trials (GOG182, ICON5) have been conducted to add a third drug to the chemotherapeutic regimen in an attempt to increase overall survival (OS) (7). However, despite an increase in the number of therapies, the clinical judgment about treatment choices in recurrent cases has become even more complex. In this regard, the results of clinical trials and observational studies are becoming increasingly important in clinical decision making on managing the advanced stage disease.

Clinical management of ovarian cancer, just like other malignancies, has evolved from a single agent to a combination therapy. A number of studies have been conducted to compare several available chemotherapeutic options in an attempt to find an appropriate chemotherapeutic option for patients with recurrent disease (8, 9). Among the South Asian countries, ovarian cancer is reported to be higher in Pakistan (10, 11) and is the third most common malignancy in Pakistani women (12). Very few studies, prospective or observational, evaluated and compared clinical responses of seven available chemotherapeutic regimens used in the treatment of recurrent ovarian cancer patients. The present study is the first report that has compared the clinic-pathological characteristics, clinical responses, therapy compliance and toxicity of several chemo-therapeutic agents in recurrent ovarian cancer patients of Lahore, Pakistan.

EXPERIMENTAL

Ethical approval

The study was duly approved by the Ethical Committee of Clinical Research, University College of Pharmacy, University of the Punjab, Lahore, Pakistan, and the Hospital Committee of Ethics on Human Research of the Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan.

Study design and population

The observational study was designed by enrolling a total of 251 recurrent ovarian cancer patients from Lahore, Pakistan. The study period was six months, from August 2015 to January 2016, in a specialized cancer care hospital. Convenient judgmental sampling was used to enroll patients to avoid missing data. Data was retrieved from the hospital information system (HIS). Study sample size was 181, calculation based on ovarian cancer prevalence in Pakistan, *i.e.*, 13.6 % (13) using 95 % confidence interval and 5 % margin of

error. However, more patients were enrolled for improved reliability and statistical power. Enrolled OC patients were segregated into 7 chemo-arms, *i.e.*, paclitaxel (PTX), topotecan (TOPO), carboplatin + liposomal doxorubicin (CLD), carboplatin + gemcitabine (CG), carboplatin + paclitaxel (CP), carboplatin + docetaxel (CD), carboplatin + gemcitabine + bevacizumab (CGB).

All ovarian cancer patients with conformed diagnosis as per the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table SI) and conforming inclusion/exclusion criteria were included in the study.

Inclusion criteria. – All recurrent OC patients, above 18 years of age, irrespective of religion, race and ethnicity, disease stage, with normal hepatic and renal functions, who had given consent for their participation in research studies were included in the study.

Exclusion criteria. – Women below 18 years of age having compromised renal and hepatic functions, incomplete chemotherapy cycles and who failed to provide informed consent were excluded from the study.

Data collection

A data collection form was designed to fulfill all the necessary objectives of the study. Clinical data included patients' basic demographics, histology subtype and FIGO staging, details of chemotherapeutic protocols, patient non-compliance due to interruptions or toxicity, therapy responses and relevant laboratory findings. All treatment plans, dose, frequency and cycles, are summarized in supplementary materials (Table SI).

Outcome measures

Primary end points of the study were progression-free survival (PFS) and rate of overall survival (OS) (14). Clinical response was evaluated both by the tumor marker CA-125 levels and radiological examination using new response evaluation criteria in solid tumor (RECIST) guidelines (supplementary material, Table SII) (15). Laboratory values were assessed at a baseline and after every chemotherapy cycle. Adverse events were graded according to the NCI common terminology criteria for adverse events (NCI-CTCAE), version 3.0 (16). Patient compliance was assessed by treatment interruptions and delays due to disease progression, death and toxicity.

Data analysis

All statistical analyses were performed using Graphpad (Prism5) and SPSS (IBM, version 21). PFS and OS curves were estimated by the Kaplan-Meier method and compared using a log-rank test (17). Frequency of untoward events/deaths during chemotherapy was determined by the Cox proportional hazard model for PFS and OS (18). Laboratory mean values in all the chemotherapy protocols were compared by the analysis of variance (ANOVA). p-value of 0.05 or less was considered statistically significant.

RESULTS AND DISCUSSION

Clinical characteristics of OC patients are summarized in Table I. The median age ranged from 48.5–55 years in all therapeutic arms (Table I). Surprisingly, compared to our findings

of the early age (median 48 years) reporting of recurrent OC in women of Lahore, Pakistan, the reporting age of women was usually above 55 years in Europe and US (18, 19). It is also plausible that young women of Lahore, Pakistan, are exposed to specific or increased risks earlier in their life for an unascertained period of time of known or unknown origin. Irrespective of chemo-protocols, stage IIIC was the most frequently reported FIGO stage with the following frequency distribution within the respective arms, *i.e.*, paclitaxel (PTX): 64.2 %, topotecan (TOPO): 42.4 %, carboplatin + liposomal doxorubicin (CLD): 42.8 %, carboplatin + gemcitabine (CG): 66.6 %, carboplatin + paclitaxel (CP): 52.2 %, carboplatin + docetaxel (CD): 53.3 % and carboplatin + gemcitabine + bivacizumab (CGB): 60.3 %, followed by stage IV (Table I). Likewise, papillary serous was the most common histological stage (PTX: 27.2 %, TOPO: 39.3 %, CLD: 24.0 %, CG: 16.6 %, CP: 16.7 %, CD: 13.3 % and CGB: 30.0 %), followed by poorly differentiated histology (Table I). The above mentioned findings corroborate many other reports (20, 21), suggesting that irrespective of ethnicity and geographical region, ovarian cancer clinical presentations exhibit minimal differences.

Lately, with the introduction of paclitaxel (21), carboplatin plus paclitaxel has become the standard combination therapy in advanced and recurrent ovarian cancer (platinum sensitive) (22, 23). In a systematic review, Fung-Kee-Fung *et al.* (24) found that in five out of thirteen trials almost all patients were platinum sensitive and re-treatment with platinum based combination significantly improved PFS and OS. Combination of a platinum based drug with either paclitaxel or gemcitabine has been shown to improve the response rate in

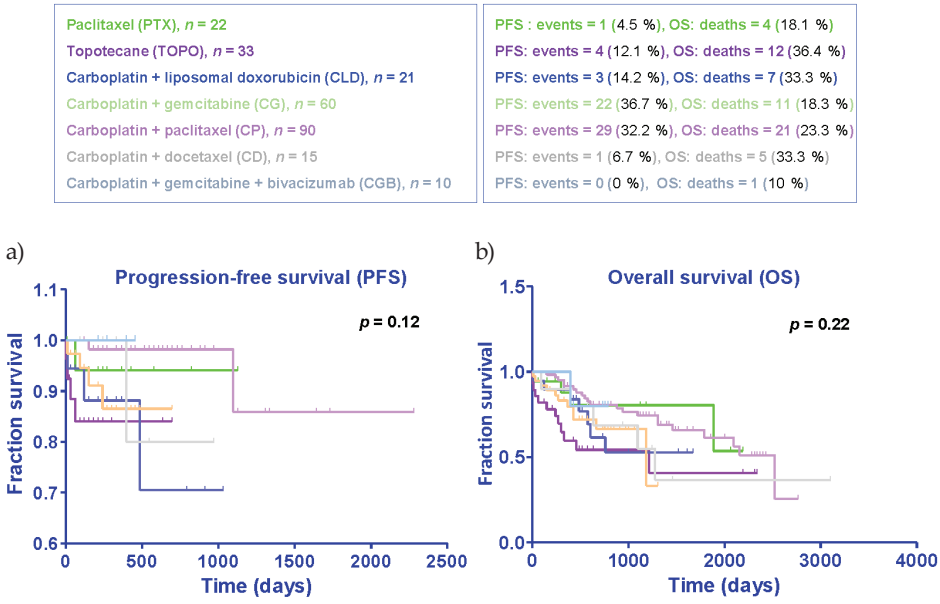

Fig. 1. Kaplan-Meier survival curves for all seven protocols: a) progression-free survival (PFS) curves for all seven chemo-protocols compared by the log-rank test. Death reported during the period of therapy was considered an event, b) overall survival curves for all seven protocols compared by the log-rank test.

Table I. Patient clinico-pathological characteristics

Characteristic	Paclitaxel (*n* = 22)	Topotecan (*n* = 33)	Carboplatin + liposomal doxorubicin (*n* = 21)	Carboplatin + gemcitabine (*n* = 60)	Carboplatin + paclitaxel (*n* = 90)	Carboplatin + docetaxel (*n* = 15)	Carboplatin + gemcitabine + bevacizumab (*n* = 10)
Patient clinico-pathological characteristics (*n*, %)							
Median age (range)	51 (20–65)	55 (18–70)	51 (32–66)	49.5 (20–61)	50 (20–68)	49 (29–60)	48.5 (33–64)
Marital status							
Married	21 (95)	32 (97)	20 (95)	57 (95)	78 (87)	14 (93)	10 (100)
Unmarried	1 (5)	1 (3)	1 (5)	3 (5)	12 (13)	1 (7)	0 (0)
FIGO stage							
IA	0	0	1 (5)	2 (3)	5 (5)	0	0
IB	0	0	1 (5)	2 (3)	0	2 (13)	0
IC	1 (5)	1 (3)	0	2 (3)	7 (8)	0	0
IIA	0	0	1 (5)	1 (2)	6 (5)	1 (7)	1 (10)
IIB	0	0	1 (5)	2 (3)	7 (8)	0	0
IIIA	0	1 (3)	2 (10)	0	1 (1)	1 (7)	0
IIIB	1 (5)	0	1 (5)	1 (2)	2 (2)	1 (7)	0
IIIC	14 (64)	14 (42)	9 (42)	40 (67)	47 (52)	8 (53)	6 (60)
IV	6 (27)	13 (40)	5 (23)	10 (17)	15 (17)	2 (13)	3 (30)
Missing	0	4 (12)	0	0	0	0	0
Histo-pathology							
Endometrioid	2 (9)	1 (3)	3 (14)	11 (18)	17 (18)	2 (13)	0
Poorly differentiated	7 (32)	7 (21)	5 (24)	7 (12)	19 (21)	2 (13)	2 (20)
Serous	1 (4)	2 (6)	2 (9)	7 (12)	11 (12)	2 (13)	3 (30)
Papillary serous	6 (27)	13 (39)	7 (33)	15 (25)	19 (21)	5 (33)	2 (20)
High grade serous	3 (14)	1 (3)	1 (5)	11 (18)	5 (6)	3 (20)	3 (30)
Mucinous	0	4 (12)	0	0	5 (6)	1 (7)	0
Clear cell	2 (9)	3 (9)	1 (5)	4 (7)	6 (7)	0	0
Missing	1 (4)	2 (6)	2 (9)	5 (8)	8 (9)	0	0

FIGO – International Federation of Gynecology and Obstetrics

Table II. Clinical response to chemotherapeutic protocols according to RECIST

Characteristic	Paclitaxel (n = 22)	Topotecan (n = 33)	Carboplatin+ liposomal doxorubicin (n = 21)	Carboplatin+ gem-citabine (n = 60)	Carboplatin+ paclitaxel (n = 90)	Carboplatin+ docetaxel (n = 15)	Carboplatin+ gem-citabine+ bevacizumab (n = 10)
Response to chemotherapy: n (%)							
After 3 cycles							
PR	11 (50)	10 (30)	11 (52)	31 (52)	57 (63)	5 (33)	8 (80)
CR	1 (4)	–	1 (5)	2 (3)	16 (18)	–	–
SD	5 (23)	6 (18)	6 (29)	11 (18)	11 (12)	6 (41)	2 (20)
PD	4 (18)	12 (36)	3 (14)	7 (12)	2 (3)	2 (13)	–
Missing	1 (4)	5 (15)	–	9 (15)	4 (4)	2 (13)	–
After 6 cycles							
PR	8 (36)	6 (18)	6 (28)	19 (31)	19 (21)	4 (27)	3 (30)
CR	3 (13)	1 (3)	3 (14)	4 (7)	47 (52)	3 (20)	1 (10)
SD	2 (9)	4 (12)	4 (19)	12 (20)	10 (11)	3 (20)	5 (50)
PD	6 (27)	19 (57)	5 (24)	19 (32)	11 (12)	3 (20)	1 (10)
Missing	3 (14)	3 (9)	3 (14)	6 (10)	3 (3)	2 (13)	–

CR – complete response, PD – progressive disease, PR – partial response, RECIST – response evaluation criteria in solid tumors, SD – stable disease

patients with recurrent ovarian cancer (9, 22). In our study, clinical response to chemotherapy protocols was assessed according to RECIST (supplementary material, Table SII). After the 3rd cycle, partial response (PR) was observed in 62 % patients belonging to CP and CGB arms while it was ~50 % in paclitaxel, CLD and CG arms (Table II). After the 3rd cycle, stable disease (SD) frequency was observed in 40 % patients in CD, 28.5 % in CLD and 22.7 % in the paclitaxel arm. After the 6th cycle, CR frequency improved slightly in all the treatment arms – more markedly in the CP (52 %) arm, but with reduced PR (Table II). Progressive disease (PD) frequency increased markedly in paclitaxel (27 %), topotecan (57 %), CLD (23.8 %) and CG (31.7 %) arms (Table II). More recently, the CD combination has been employed in platinum sensitive recurrent ovarian cancer with the overall response rate of 70 %, CR of 28 % and median PFS of 12.4 months (25) – complemented by another report with CR of 38 % employing CD regimen (26), but with hematological toxicities, *i.e.*, neutropenia. In our data, after the 6th cycle, compared to the CP arm (CR, 52 %), the CD arm demonstrated CR in 20 % of patients, but also with higher hematological toxicities. Similarly to our findings with 52 % complete response (CR) in the CP arm, Gibson *et al*. (27) found CR of 40–60 % in patients on CP regimen.

As shown in Fig. 1, no significant differences were observed between patients' survival PFS (log-rank test, $p = 0.12$) and OS (log-rank test, $p = 0.22$) on various chemo-protocols (Fig. 1). The highest median progression-free survival (PFS) was observed in the CP arm (15 months) followed by CGB (13 months), CD (11.5 months), CLD (9 months), CG (8 months), PTX (7.5 months) and TOPO (5 months) arms. Nevertheless, the median overall survival was highest in the CD arm (21 months) and lowest in the CG arm (8 months). Similarly to our findings, the ICON4/OVAR2.2 trial demonstrated that addition of paclitaxel to carboplatin extended the PFS and OS in ovarian cancer patients (28). However, when we compared PFS and OS in CP and CG arms, no significant differences were observed; yet, the maximum non-compliance frequency was observed in the CG (81.6 %) arm, presumably due to grade 1–3 hematological toxicities. Likewise, the AGO-OVAR-led intergroup trial in recurrent ovarian cancer patients compared CG with CP regimens, demonstrating similar PFS with no improvement in OS, but with treatment delays that were attributed to myelo-suppression (29). Other studies reported that CLD was as efficacious as CP (20, 30); however, in the MITO-2 trial, despite no improvements in PFS and OS, pegylated liposomal doxorubicin (PLD) plus carboplatin was suggested as an alternative first line chemo regimen comparable to the CP regimen (19) taking into account the toxicity profiles and observed confidence intervals.

Table III. Patient compliance for various chemotherapy protocols

Chemotherapy Compliance during Treatment							
Characteristics	Paclitaxel (n = 22)	Topotecan (n = 33)	Carboplatin + liposomal doxorubicin (n = 21)	Carboplatin + gemcitabine (n = 60)	Carboplatin + paclitaxel (n = 90)	Carboplatin + docetaxel (n = 15)	Carboplatin + gemcitabine + gevacizumab (n = 10)
Cause of treatment interruption (n, %)							
Missing information	–	–	–	–	3 (3)	1 (7)	1 (10)
Progression/ death	3 (14)	14 (42)	3 (14)	10 (16)	5 (6)	3 (20)	–
Toxicity	1 (4)	2 (6)	4 (19)	37 (62)	29 (32)	7 (46)	6 (60)
Others	0	6 (18)	7 (20)	12 (20)	–	2 (13)	1 (10)
Toxicity delays							
2nd cycle	0	0	1	20	4	2	2
3rd cycle	0	1	2	5	6	2	3
4th cycle	0	1	0	3	5	1	0
5th cycle	1	0	1	6	9	0	1
6th cycle	0	0	0	3	5	0	0
Non-compliance (%)	1/22 (4)	8/33 (24)	11/21 (52)	49/60 (81)	29/90 (32)	9/15 (60)	7/10 (70)

Percent of non-compliance was estimated based on toxicity delays in each cycle and any other reason of interruption (not reporting to clinic) in treatment without taking into account reported death.

As for therapy compliance, the proportion of treatment delays due to disease progression/deaths was highest in topotecan (42.4 %), while due to toxicity, it was highest in the carboplatin + gemcitabine arm (61.6 %) (Table III). In the combination regimen, the highest treatment non-compliance was observed in the carboplatin + gemcitabine arm (81.6 %), while the CP arm exhibited the lowest non-compliance frequency (32.2 %) (Table III). Thus, we observed better compliance in mono therapy (paclitaxel: 4.54 %, topotecan: 24.2 %) compared to combination therapy; nevertheless, no single therapy (topotecan or paclitaxel) exhibited clinical edge over the combination therapy, but there were subtle differences in treatment-related adverse events. However, toxicity with topotecan is subject to several factors, such as dose schedule adjustments based on the patient's prior treatment, radiation therapy, extent of cumulative myelo-suppression with prior agents (31). More recently, bevacizumab has been used in combination with other chemotherapeutic agents in recurrent ovarian cancer (32) with improved tolerability and encouraging efficacy. In the OCEANS trial, PFS was improved in the CGB arm compared to CG arm with high grade hypertension in the bevacizumab arm, duly supported by our findings of grade 2 hypertension in 30 % subjects belonging to the CGB arm (17).

In the multivariate analysis for PFS and OS, only topotecan was significantly associated with higher rate of events [for PFS: Cox proportional hazard ratio (HR) was 20.22, confidence interval (CI) 2.16–188.94, $p = 0.008$, for OS: HR was 3.83; CI 1.804–8.119, $p = 0.0005$) (Table IV)]. Notably, significant differences were observed in laboratory values among

Table IV. Cox proportional hazard model for PFS and OS

Factor	N	Hazard ratio	95 % CI	*p*-value
Protocols	Cox proportional hazard model for progression free survival (PFS)			
Carboplatin + paclitaxel	90			Reference
Paclitaxel	22	–	–	–
Topotecan	33	20.2	(2.16–188.94)	0.008*
Carboplatin + liposomal doxorubicin	21	5.8	(0.36–93.99)	0.21
Carboplatin + gemcitabine	60	8.1	(0.72–89.54)	0.08
Carboplatin + docetaxel	15	6.3	(0.64–62.07)	0.11
Carboplatin + gemcitabine + bevacizumab	10	–	–	–
Protocols	Cox proportional hazard model for overall survival (OS)			
Carboplatin + paclitaxel	90			Reference
Paclitaxel	22	0.9	(0.33–2.86)	0.96
Topotecan	33	3.8	(1.80–8.11)	0.0005**
Carboplatin + liposomal doxorubicin	21	1.3	(0.44–3.88)	0.61
Carboplatin + gemcitabine	60	1.3	(0.54–3.40)	0.51
Carboplatin + docetaxel	15	1.3	(0.60–3.25)	0.43
Carboplatin + gemcitabine + bevacizumab	10	0.9	(0.12–7.22)	0.96

*$p \leq 0.05$, **$p \leq 0.001$
(–) – no output recorded/obtained in the model.

various chemo-protocols, such as platelets, neutrophils, hemoglobin, albumin, AST and ALT ($p < 0.025$) (supplementary material, Table SIII). Very few grade-4 toxicities, hematological and hepatic, were observed in paclitaxel, CG and CP treatment arms (supplementary material, Table SIV).

CONCLUSIONS

In conclusion, our data suggest that CP chemo-protocol demonstrated better median PFS and OS in recurrent ovarian cancer patients, yet statistically non-significant, along with maximum partial and complete responses after the 3rd and 6th cycles, resp. In the combination regimen, CP was associated with the lowest non-compliance, while the highest non-compliance was observed in the CG arm. However, the CP arm was associated with considerable hematological and abdominal adverse effects in addition to peripheral neuropathy and fatigue. Topotecan was associated with significantly higher propensity of having therapy related events/deaths.

Acknowledgements. – The authors are grateful to the hospital administration and patients for their kind cooperation and informed consent, helpful in completing the study. Supplementary materials are available upon request.

REFERENCES

1. B. M. Reid, J. B. Permuth and T. A. Sellers, Epidemiology of ovarian cancer: a review, *Cancer Biol. Med*. **14** (2017) 9–32; https://doi.org/10.20892/j.issn.2095-3941.2016.0084
2. J. Permuth-Wey and T. A. Sellers, 20. *Epidemiology of Ovarian Cancer*, in *Cancer Epidemiology: Modifiable Factors* (Ed. M. Verma)/Series: *Methods of Molecular Biology* **472** (2009) 413–437, Springer, New York 2009; https://doi.org/10.1007/978-1-60327-492-0_20
3. J. Ledermann, F. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo and C. Sessa (ESMO guidelines working group), *Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up*, *Ann. Oncol.* **24** (Suppl. 6) **(**2013**)** vi24-vi32. https://doi.org/10.1093/annonc/mdt333
4. F. Raja, N. Chopra and J. Ledermann, Optimal first-line treatment in ovarian cancer, *Ann. Oncol*. **23** (Suppl. 10) (2012) x118-x127; https://doi.org/10.1093/annonc/mds315
5. M. Cristea, E. Han, L. Salmon and R. J. Morgan, Review: Practical considerations in ovarian cancer chemotherapy, *Ther. Adv. Med. Oncol*. **2** (2010) 175–187; https://doi.org/10.1177/1758834010361333
6. M. Kyrgiou, G. Salanti, N. Pavlidis, E. Paraskevaidi and J. P. Ioannidis, Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments, *J. Natl. Cancer Inst*. **98** (2006) 1655–1663; https://doi.org/10.1093/jnci/djj443
7. M. A. Bookman (Ed.), GOG0182-ICON5: 5-arm phase III randomized trial of paclitaxel (P) and carboplatin (C) vs combinations with gemcitabine (G), PEG-lipososomal doxorubicin (D), or topotecan (T) in patients (pts) with advanced-stage epithelial ovarian (EOC) or primary peritoneal (PPC) carcinoma, *J. Clin. Oncol*. **24** (Suppl.) (2006) 5002–5002 (*ASCO Annual Meeting Proceedings 2006*); https://doi.org/10.1200/jco.2006.24.18_suppl.5002
8. J. A. Ledermann and R. S. Kristeleit, Optimal treatment for relapsing ovarian cancer, *Ann. Oncol*. **21** (Suppl. 7) (2010) vii218-222; https://doi.org/10.1093/annonc/mdq377
9. D. S. Dizon, M. L. Hensley, E. A. Poynor, P. Sabbatini, C. Aghajanian, A. E. Hummer. D. R. Venkatraman and R. Spriggs, Retrospective analysis of carboplatin and paclitaxel as initial second-line

therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer, *J. Clin. Oncol*. **20** (2002) 1238–1247; https://doi.org/ 10.1200/JCO.2002.20.5.1238

10. M. U. Rashid, A. Zaidi, D. Torres, F. Sultan, A. Benner, B. Naqvi, A. R. Shakoori, A. Seidel-Renkert, H. Farooq, S. Narod, A. Amin and U. Hamann, Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients, *Int. J. Cancer* **119** (2006) 2832–2839; https://doi.org/10.1002/ijc.22269
11. M. A. Moore, Y. Ariyaratne, F. Badar, Y. Bhurgri, K. Datta, A. Mathew, P. Gangadharan, A. Nandakumar, K. K. Pradhananga, M. H. Talukder, B. B. Yeole and T. Sobue, Cancer epidemiology in South Asia - past, present and future, *Asian Pac. J. Cancer Prev.* **11** (Suppl. 2) (2010) 49–66.
12. Y. Bhurgri, Karachi cancer registry data - implications for the National Cancer Control Program of Pakistan, *Asian Pac. J. Cancer Prev.* **5** (2004) 77–82.
13. Ovarian cancer second most common type in Pakistan, The Daily News 2016, https://www.thenews.com.pk/print/105779-Ovarian-cancer-second-most-common-type-in Pakistan; last access date July 15, 2018.
14. P. Cheema and R. Burkes, Overall survival should be the primary endpoint in clinical trials for advanced non-small-cell lung cancer, *Curr. Oncol.* **20** (2013) e150; https://doi.org/10.3747/co.20.1226
15. E. Eisenhauer, P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe and J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* **45** (2009) 228–247; https://doi.org/10.1016/j.ejca.2008.10.026
16. S. Zhang, F. Liang and I. Tannock, Use and misuse of common terminology criteria for adverse events in cancer clinical trials, *BMC Cancer* **16** (2016) Article ID 392 (6 pages); https://doi.org/10.1186/s12885-016-2408-9
17. C. Aghajanian, S. V. Blank, B. A. Goff, P. L. Judson, M. G. Teneriello, A. Husain, M. A. Sovak, J. Yi and L. R. Nycum, OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, *J. Clin. Oncol.* **30** (2012) 2039–2045; https://doi.org/10.1200/JCO.2012.42.0505
18. M. Kyrgiou, G. Salanti, N. Pavlidis, E. Paraskevaidis and J. P. Ioannidis, Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments, *J. Natl. Cancer Inst.* **98** (2006) 1655–1663; https://doi.org/10.1093/jnci/djj443
19. S. Pignata, G. Scambia, G. Ferrandina, A. Savarese, R. Sorio, E. Breda, V. Gebbia, P. Musso, L. Frigerio, P. Del Medico, A. V. Lombardi, A. Febbraro, P. Scollo, A. Ferro, S. Tamberi, A. Brandes, A. Ravaioli, M. R. Valerio, E. Aitini, D. Natale, L. Scaltriti, S. Greggi, C. Pisano, D. Lorusso, V. Salutari, F. Legge, M. Di Maio, A. Morabito, C. Gallo and F. Perrone, Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial, *J. Clin. Oncol.* **29** (2011) 3628–3635; https://doi.org/10.1200/JCO.2010.33.8566
20. R. S. Suidan, C. M. St Clair, S. J. Lee, J. N. Barlin, K. C. Long Roche, E. J. Tanner, Y. Sonoda, R. R. Barakat, O. Zivanovic and D. S. Chi, A comparison of primary intraperitoneal chemotherapy to consolidation intraperitoneal chemotherapy in optimally resected advanced ovarian cancer, *Gynecol. Oncol*. **134** (2014) 468–472; https://doi.org/10.1016/j.ygyno.2014.07.090
21. M. J. Piccart, K. Bertelsen, K. James, J. Cassidy, C. Mangioni, E. Simonsen, G. Stuart, S. Kaye, I. Vergote, R. B. R. Grimshaw, R. J. Atkinson, K. D. Swenerton, C. Trope, M. Nardi, J. Kaern, S. Tumolo, P. Timmers, J. Roy, F. Lhoas, B. Lindvall, M. Bacon, A. Birt, J. E. Andersen, B. Zee, J. Paul, B. Baron and S. Pecorelli, Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results, *J. Natl. Cancer Inst.* **92** (2000) 699–708; https://doi.org/10.1093/jnci/92.9.699

22. A. du Bois, H. J. Lück, W. Meier, H. P. Adams, V. Möbus, S. Costa, T. Bauknecht, B. Richter, M. Warm, W. Schröder, S. Olbricht, U. Nitz, C. Jackisch, G. Emons, U. Wagner, W. Kuhn and J. Pfisterer, A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer, *J. Natl. Cancer Inst.* **95** (2003) 1320–1329; doi 10.1093/jnci/djg036
23. R. F. Ozols, B. N. Bundy, B. E. Greer, J. M. Fowler, D. Clarke-Pearson, R. A. Burger, R. S. Mannel, K. DeGeest, E. M. Hartenbach and R. Baergen, Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study, *J. Clin. Oncol.* **21** (2003) 3194–3200; https://doi.org/10.1200/jco.2003.02.153
24. M. Fung-Kee-Fung, T. Oliver, L. Elit, A. Oza, H. W. Hirte and P. Bryson, Optimal chemotherapy treatment for women with recurrent ovarian cancer, *Curr. Oncol.* **14** (2007) 195–208.
25. Y. Wang, J. Herrstedt, H. Havsteen, R. DePoint Christensen, M. R. Mirza, B. Lund, J. Maenpaa and G. Kristensen, A multicenter, non-randomized, phase II study of docetaxel and carboplatin administered every 3 weeks as second line chemotherapy in patients with first relapse of platinum sensitive epithelial ovarian, peritoneal or fallopian tube cancer, *BMC Cancer* **14** (2014) Article ID 937 (7 pages); https://doi.org/10.1186/1471-2407-14-937
26. L. A. Holmberg, P. Paley and B. Goff, Docetaxel and carboplatin as salvage therapy for first-relapsed, platinum-sensitive, stage III/IV advanced ovarian cancer, *Clin. Ovar. Other Gynecol. Cancer* **7** (2014) 13–17; https://doi.org/10.1016/j.cogc.2014.12.005
27. J. M. Gibson, S. Alzghari, C. Ahn, H. Trantham and N. M. La-Beck, The role of pegylated liposomal doxorubicin in ovarian cancer: a meta-analysis of randomized clinical trials, *Oncologist* **18** (2013) 1022–1031; https://doi.org/ 10.1634/theoncologist.2013-0126
28. M. Parmar, J. Ledermann, N. Colombo, A. du Bois, J. F. Delaloye, G. B. Kristensen, S. Wheeler, A. M. Swart, W. Qian, V. Torri, I. Floriani, G. Jayson and A. Lamont, C. Tropé, Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial, *Lancet* **361** (2003) 2099–2106; https://doi.org/10.1016/S0140-6736(03)13718-X
29. J. Pfisterer, M. Plante, I. Vergote, A. du Bois, H. Hirte, A. J. Lacave, U. Wagner, A. Stähle, G. Stuart, R. Kimmig, S. Olbricht, T. Le, J. Emerich, W. Kuhn, J. Bentley, C. Jackisch, H. J. Lück, J. Rochon, A. H. Zimmermann and E. Eisenhauer, 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.* **24** (2006) 4699–4707; https://doi.org/10.1200/JCO.2006.06.0913
30. D. Bafaloukos, H. Linardou, G. Aravantinos, C. Papadimitriou, A. Bamias, G. Fountzilas, H. P. Kalofonos, P. Kosmidis, E. Timotheadou, T. Makatsoris, E. Samantas, E. Briasoulis, C. Christodoulou, P. Papakostas, D. Pectasides and A. M. Dimopoulos, A randomized phase II study of carboplatin plus pegylated liposomal doxorubicin versus carboplatin plus paclitaxel in platinum sensitive ovarian cancer patients: a Hellenic Cooperative Oncology Group study, *BMC Med.* **8** (2010) Article ID 3 (12 pages); https://doi.org/10.1186/1741-7015-8-3
31. C. J. Dunton, Management of treatment-related toxicity in advanced ovarian cancer, *Oncologist* **7** (Suppl. 5) (2002) 11–19.
32. K. Kudoh, M. Takano, H. Kouta, R. Kikuchi, T. Kita, M. Miyamoto, A. Watanabe, M. Kato, T. Goto and Y. Kikuchi, Effects of bevacizumab and pegylated liposomal doxorubicin for the patients with recurrent or refractory ovarian cancers, *Gynecol. Oncol.* **122** (2011) 233–237; https://doi.org/10.1016/j.ygyno.2011.04.046

Supplementary Material

Table SI. Chemotherapy regimens used in Shaukat Khanum Memorial Cancer and Research Hospital for patients with ovarian cancer

Chemotherapy regimen	Dose and cycles	Number of patients (total, $n = 251$)
Paclitaxel (PTX)	Weekly paclitaxel 80 mg m^{-2} IV over 1 hour	22
Topotecan (TOPO)	Topotecan 1.25–1.5 mg m^{-2} as single agent IV over 30 minutes on days 1–5; every 21 days	33
Carboplatin + liposomal doxorubicin (CLD)	Carboplatin AUC 5 IV push plus liposomal doxorubicin 30 mg m^{-2} IV over 30 minutes; every 28 days for six cycles	21
Carboplatin + gemcitabine (CG)	Gemcitabine 1000 mg m^{-2} IV over 30 minutes on day 1 and 8 plus carboplatin AUC 4–5 IV over 1 hour on day 1; every 21 days for six cycles	60
Carboplatin + paclitaxel (CP)	Paclitaxel 175 mg m^{-2} *i.v.* over 3 hours plus carboplatin (AUC 5–7.5) over 30 minutes on day 1; every 21 days for six cycles	90
Carboplatin + docetaxel (CD)	Docetaxel 75 mg m^{-2} IV over 1 hour plus carboplatin (AUC 5) IV over 1 hour on day 1; every 21 days up to six cycles	15
Carboplatin + gemcitabine + bevacizumab (CGB)	Gemcitabine 1000 mg m^{-2} IV over 30 minutes on day 1 and 8 plus carboplatin AUC 4–5 IV push on day 1; every 21 days for 6 cycles plus bevacizumab 15 mg kg^{-1} IV on day 1 prior to gemcitabine and carboplatin and continued until disease progression or unbearable toxicity	10

Table SII. Response evaluation criteria in solid tumors (RECIST)

Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response (PR)	At least a 30 % decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20 % increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more lesions is also considered progression.

Table SIII. Biochemical laboratory values for all chemotherapeutic protocols

Laboratory value	Paclitaxel (n = 22)	Topotecan (n = 33)	Carboplatin + liposomal doxorubicin (n = 21)	Carboplatin + gemcitabine (n = 60)	Carboplatin + paclitaxel (n = 90) carboplatin + paclitaxel (n = 90)	Carboplatin + docetaxel (n = 15)	Carboplatin + gemcitabine + bevacizumab (n = 10)	p-value
Median platelet count (range)	266 (196–374.1)	271 (37.7–633.5)	240 (23.2–661.3)	207 (37.3–635.9)	246 (6.1–1090.1)	192 (122.7–342.5)	228 (83.7–305.7)	0.0005**
Median albumin (range)	4 (2.6–4.8)	4 (1.9–4.7)	4 (2.7–4.7)	4 (2.4–4.7)	4 (2.8–5.1)	4 (2.3–4.8)	4 (3.1–4.5)	0.0005**
Hemoglobin (range)	12 (8.7–14.5)	10 (5.2–12.2)	11 (8.7–12.8)	10 (7.9–11.9)	12 (8.5–13.1)	10 (9.4–12.9)	11 (8.7–14.6)	0.0005**
WBCs (range)	6 (3.2–12.2)	6 (1.2–20.5)	6 (3.3–15.8)	5 (1.8–15.6)	7 (3.2–382.5)	6 (4.2–8.6)	7 (4.8–10.7)	0.89
Median neutrophils (%) (range)	54 (28.5–87.1)	54 (23.2–81.2)	45 (24.2–67.1)	47 (25.7–79.4)	57 (35.6–71.7)	50 (36.9–72.6)	57 (39.7–68.3)	0.0005**
Median creatinine (range)	0.6 (0.3–2.4)	0.6 (0.3–1.6)	0.6 (0.1–1.1)	0.5 (0.2–2.1)	0.6 (0.3–2.8)	0.6 (0.4–0.8)	0.6 (0.5–1.9)	0.36
Median bilirubin (range)	0.2 (0.17–1.1)	0.4 (0.9–26.4)	0.2 (0.2–1.6)	0.3 (0.2–11.8)	0.3 (0.1–0.7)	0.2 (0.2–0.9)	0.2 (0.18–0.3)	0.34
Median AST (range)	25 (14.6–99.3)	26 (13.9–216.8)	24 (10.5–4)	37 (16.8–245.7)	24 (9.5–130.1)	22 (15.3–37.2)	29 (16.1–122.8)	0.024*
Median ALT (range)	25 (8.5–87.7)	23 (10.7–154.7)	22 (11.9–57.4)	35 (9.1–140.3)	23 (10.3–158.8)	21 (13.4–47.2)	26 (22.5–125.1)	0.003*
Median CA-125 (range)	47 (3.2–40698.2)	157 (6.7–3504.2)	195 (6.1–9149.9)	183 (6.4–15137.1)	85 (1.6–2988.1)	75 (10.7–5031.5)	216 (10.1–4265.7)	0.14

CA125 – cancer antigen-125, WBC – white blood cell, ALT – alanine transaminase, AST – aspartate aminotransferase
* $p \leq 0.05$, ** $p \leq 0.001$

Table SIV. Toxicity grading (as per NCI-CTC) according to chemotherapy regimens

Toxicity	Paclitaxel (n = 22)	Topotecan (n = 33)	Carboplatin + liposomal doxorubicin (n = 21)	Carboplatin + gemcitabine (n = 60)	Carboplatin + paclitaxel (n = 90)	Carboplatin + docetaxel (n = 15)	Carboplatin + gemcitabine + bevacizumab (n = 10)
Toxicity grading (n, %)							
Hematological							
Anemia							
Grade 1	10 (46)	6 (18)	7 (33)	18 (30)	45 (50)	3 (20)	7 (70)
Grade 2	1 (4)	13 (39)	7 (33)	22 (37)	24 (27)	7 (47)	2 (20)
Grade 3	–	2 (6)	–	9 (15)	–	1 (7)	–
Leukopenia							
Grade 1	4 (18)	1 (3)	2 (10)	9 (15)	14 (16)	1 (7)	1 (10)
Grade 2	1 (4)	1 (3)	2 (10)	8 (13)	2 (2)	–	1 (10)
Grade 3	0	–	–	1 (2)	1 (1)	–	–
Grade 4	1 (4)	–	–	–	–	–	–
Thrombocytopenia							
Grade 1	–	1 (3)	4 (19)	11 (18)	11 (12)	7 (47)	3 (30)
Grade 2	–	–	–	2 (3)	2 (2)	–	–
Grade 3	–	–	–	1 (2)	1 (1)	–	1 (10)
Grade 4	–	–	–	1 (2)	–	–	–
Neutropenia							
Grade 1	4 (18)	–	3 (14)	10 (17)	10 (11)	1 (7)	1 (10)
Grade 2	2 (9)	4 (12)	3 (14)	13 (22)	7 (8)	–	1 (10)
Grade 3	–	1 (3)	1 (5)	4 (6)	1 (1)	–	2 (20)
Grade 4	–	–	–	–	1 (1)	–	–
Renal toxicity							
Creatinine							
Grade 1	–	6 (18)	–	3 (5)	3 (3)	1 (7)	–
Grade 2	–	–	–	1 (2)	2 (2)	–	–
Hepatic toxicity							
Bilirubin							
Grade 1	–	–	1 (5)	–	–	–	–
Grade 2	–	–	1 (5)	–	1 (1)	–	–
Grade 4	–	–	–	1 (2)	–	–	–
GIT events							
Abdominal pain							
Grade 1	1 (5)	2 (6)	1 (5)	10 (17)	5 (6)	3 (20)	4 (40)
Grade 2	–	–	–	3 (5)	–	–	–
Abdominal distension							
Grade 1	2 (9)	–	2 (10)	5 (8)	2 (2)	5 (33)	–
Constipation							
Grade 1	–	4 (12)	–	4 (7)	3 (3)	–	–
Nausea							
Grade 1	1 (5)	1 (3)	1 (5)	4 (7)	9 (10)	2 (13)	4 (40)

Grade 2	–	–	–	–	–	–	–
Grade 3	–	3 (9)	–	1 (2)	1 (1)	–	–
Vomiting							
Grade 1	–	2 (6)	1 (5)	9 (15)	3 (3)	–	–
Grade 2	–	–	1 (5)	4 (7)	–	–	–
Diarrhea							
Grade 1	–	1 (3)	–	5 (8)	2 (2)	1 (7)	–
Grade 2	–	2 (6)	–	2 (3)	1 (1)	–	–
Grade 3	–	–	–	1 (2)	1 (1)	–	–
Anorexia							
Grade 1	–	1 (3)	1 (5)	2 (3)	4 (4)	1 (7)	–
Grade 2	–	1 (3)	1 (5)	1 (2)	–	–	–
Peripheral neuropathy							
Grade 1	4 (18)	1 (3)	3 (14)	4 (7)	16 (18)	1 (7)	–
Grade 2	2 (9)	1 (3)	1 (5)	–	4 (4)	–	–
Grade 3	–	2 (6)	–	–	2 (2)	–	–
Fatigue							
Grade 1	3 (14)	3 (9)	6 (29)	12 (20)	10 (11)	6 (7)	4 (40)
Grade 2	–	1 (3)	–	2 (3)	2 (2)	–	–
Grade 3	–	–	1 (5)	–	–	–	–
Pulmonary toxicity							
Cough							
Grade 1	–	2 (6)	2 (2)	5 (8)	6 (7)	–	4 (40)
Grade 2	–	–	3 (14)	–	–	–	–
Cardiovascular events							
Hypertension							
Grade 1	–	–	–	1 (2)	2 (2)	–	1 (10)
Grade 2	–	–	–	–	–	–	3 (30)
Tachycardia							
Grade 1	–	1 (3)	–	3 (5)	1 (1)	–	–
Others							
Mucositis							
Grade 1	–	–	–	3 (5)	3 (3)	1 (2)	3 (30)
Grade 2	–	–	–	–	1 (1)	–	–
Rash							
Grade 1	–	–	–	4 (7)	1 (1)	2 (13)	1 (10)
Depression							
Grade 1	2 (9)	–	–	–	2 (2)	–	–
Grade 2	–	–	2 (2)	–	–	–	–
Fever							
Grade 1	–	2 (6)	–	–	1 (1)	–	2 (20)
Bleeding							
Grade 1	–	2 (6)	–	–	–	–	–
Infection during therapy							
Yes	–	1 (3)	6 (29)	3 (5)	18 (20)	1 (7)	1 (10)
No	–	–	–	–	–	–	–

NCI-CTC – National Cancer Institute Common Toxicity Criteria