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Effects of sequential paclitaxel–carboplatin followed by gemcitabine-based chemotherapy compared with paclitaxel-carboplatin therapy administered to patients with advanced epithelial ovarian cancer

A retrospective, STROBE-compliant study

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Abstract

We aimed to compare the efficacy of paclitaxel and carboplatin followed by gemcitabine-based combination chemotherapy with paclitaxel–carboplatin for treating advanced epithelial ovarian cancer in this retrospective, STROBE-compliant study. Patients' tolerance to treatment was also assessed.

We retrospectively analyzed the records of 178 women who underwent initial optimal debulking surgery between January 2003 and December 2011 to treat FIGO stage IIIc epithelial ovarian cancer. Patients in arm 1 (n = 88) received 4 cycles of paclitaxel and carboplatin followed by 2 to 4 cycles of gemcitabine-based combination chemotherapy. Patients in arm 2 (n = 90) received 6 to 8 cycles of paclitaxel and carboplatin. The granulocyte-colony stimulating factor was administered prophylactically to all patients.

The median follow-up for both arms was 62 months. Medianprogression-free survival (PFS) between arms 1 and 2 (28 and 19 months [$P = 0.003$]) as well as 5-year OS (34.1% and 18.9% [$P = 0.021$]) differed significantly. The neurotoxicity rate was significantly higher in arm 2 than in arm 1 (45.2% vs 27.1%, $P = 0.026$). There was no significant difference between study arms in hematological toxicity.

The sequential regimen significantly improved PFS and 5-year OS with tolerable toxicity compared with the single regimen, and offers an alternative for treating patients with advanced epithelial ovarian cancer.

Abbreviations: ADM = adriamycin, ANC = absolute neutrophil count, CBC = complete blood counts, CR = complete response, CR+PR = overall response rate, CT = computed tomography, EOC = epithelial ovarian cancer, EPI = epirubicin, FIGO = International Federation of Gynaecology and Obstetrics, G-CSF = granulocyte-colony stimulating factor, GEM = gemcitabine, IFO = Ifosfamide, IP = intraperitoneal, KPS = Karnofsky performance status, OS = overall survival, PFS = progression-free survival, PR = partial response, SD = stable disease, TC = paclitaxel and carboplatin.

Keywords: carboplatin, epithelial ovarian cancer, gemcitabine, paclitaxel, sequential chemotherapy

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death of women (14,404 deaths in the USA in 2016).[1] Most (64%) patients progress to stage III or IV[2,3] because of the absence of specific symptoms during the early stages of disease, and the lack of effective screening tools to detect early disease. The gold standard for treatment of primary advanced ovarian cancer is cytoreductive surgery, followed by chemotherapy using platinum–taxane combinations.[4,5] Despite standard chemotherapy consisting of paclitaxel and carboplatin, survival rates remain constant,[6] and most patients, particularly those with advanced disease, will suffer a relapse within 2 years.[7,8] Salvage chemotherapy in addition to the secondary cytoreductive surgery is often administered to patients with recurrent EOC (epithelial ovarian cancer). Unfortunately, second-line therapies are relatively ineffective for these patients, with response rates ranging from 10% to 25%,[9] and most patients succumb to their disease. Therefore, further improvements to systemic treatment approaches are urgently required.

One such approach involves incorporating potentially new noncross-resistant agents in standard first-line combinations. However, this approach may lead to increased toxic adverse events that delay treatment or reduce the tolerated dose. Norton-Simon proposed the hypothesis that sequential schedules allow optimal doses to be administered in dose-dense cycles.[10,11] Accordingly, the use of sequential chemotherapy may serve as an effective approach that allows the administration of optimal dosage and eliminates toxicity.

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Here, we evaluated treatment using sequential paclitaxel and carboplatin followed by gemcitabine-based combination chemotherapy. Gemcitabine, which is a fluorine-substituted pyrimidine antimetabolite, is theoretically an effective candidate for use in combination with other cytotoxic agents because of its unique mechanism of its action and generally acceptable toxicity. Gemcitabine inhibits DNA elongation, DNA repair enzymes, and RNA synthesis.[12] Accordingly, gemcitabine may inhibit the growth of platinum-resistant tumor cells.

Preclinical and clinical studies show that gemcitabine[13–15] and carboplatin[4,16] synergize with cisplatin, which may be explained by the inhibition by gemcitabine of platinum-induced DNA crosslink repair.[17] Phase II studies of patients with ovarian cancer demonstrate that treatment with gemcitabine alone achieves response rates of 13% to 22%, which is comparable with the response rates to other agents in a similar patient population.[18,19] Moreover, gemcitabine shows promising results with low toxicity when incorporated in triple-drug regimens or as a sequential agent.[20–22]

Ifosfamide (IFO) was chosen as a second agent in combination with paclitaxel/platinum chemotherapy because of its promising effectiveness for treating patients with ovarian cancer. Papadimitriou et al[23] previously combined ifosfamide with paclitaxel and cisplatin, obtaining an objective response rate of 85% in 26 epithelial ovarian cancer patients. Moreover, the administration of other noncross-resistant agents such as adriamycin (ADM) and epirubicin (EPI) achieved response rates of 31.6% to 65% in patients with advanced solid tumors.[24,25] What's more, ifosfamide, an oxazophosphorine alkylating agent, its metabolites can interfere with the synthesis of DNA through irreversible crosslinking with DNA. Adriamycin (ADM) is an anthracycline antibiotic that induces DNA strand breakage through DNA intercalation, and inhibition of both topoisomerase II and DNA polymerase.[24] Meanwhile, epirubicin, as isomers of adriamycin, is directly embedded into DNA base pairs, interfere with the transcription process, prevent the formation of the mRNA, thus inhibiting the synthesis of DNA and RNA. In addition, it has an inhibitory effect on topoisomerase II. So we choose one from adriamycin and epiubicin as another sequential agent. Combining these drugs with nonoverlapping cytotoxic agents theoretically maximizes the effect of each chemotherapeutic agent and reduces drug resistance.

The present study was initially conducted to evaluate the activity and tolerability of sequential administration of paclitaxel–carboplatin followed by gemcitabine-based (GEM+IFO +/–ADM/EPI) chemotherapy as first-line treatment of advanced epithelial ovarian cancer.

2. Patients and methods

2.1. Patients

Patients enrolled in this study from January 2003 to December 2011. Inclusion criteria included: (1) all patients were histologically confirmed epithelial ovarian, stage IIIc according to the International Federation of Gynaecology and Obstetrics (FIGO) classification (1988). (2) Total patients completed all planned optimal (defined as $\leq$1 cm gross residual disease) debulking surgery to minimize the tumor burden in Shandong Cancer Hospital and Institute. (3) No neoadjuvant chemotherapy was allowed before the primary debulking surgery. (4) Karnofsky performance status >70%. (5) Aged 18 to 75 years. (6) Required systemic chemotherapy but no intraperitonea (IP) chemotherapy was allowed after cytoreductive surgery. Exclusion criteria included: (1) malignancies or previous history of other malignancy within the last 5 years (except nonmelanoma skin cancer, carcinoma in situ of the cervix). (2) Documented borderline ovarian malignancies. (3) History of cardiac diseases.

So, in our study, we conducted a retrospective review of 88 patients treated with paclitaxel–carboplatin followed by gemcitabine-based chemotherapy and 91 patients who were treated with paclitaxel–carboplatin. The characteristics of patients were acquired from their medical records. The Regional Ethical Committee at Shandong cancer hospital approved our study and all patients signed informed consent prior to the study.

2.2. Treatment schedule

In arm 1 (experimental arm 1), patients received 175 mg/m^2 paclitaxel for 3 h on day 1 and carboplatin according to the area under the curve[26] (AUC) = 5–6, on day 2, or treatment was fractionated for 4 cycles during 3 to 5 days of a 21 to 28 day cycle. We next administered 2 to 4 cycles of combined chemotherapy comprising GEM+ IFO +/– ADM/ EPI. Gemcitabine (800 mg/m^2) was administered intravenously for approximately 30 minutes on days 1 and 8. IFO (1.5 g/m^2) was administered for 3 hours during the first 3 days together with mesna uroprotection, and 20% of the IFO dose was administered 0, 4, and 8 hours after IFO. ADM (40 mg/m^2) or EPI (60 mg/m^2) was infused intravenously on day 1. All study drugs were administered for 21 to 28 days.

In arm 2, (standard treatment group), carboplatin (AUC = 5–6) and paclitaxel were administered as above for 6 to 8 consecutive cycles for 21 to 28 day intervals during each cycle.

Prophylactic dexamethasone, cimetidine, and promethazine hydrochloride were prescribed to prevent potential side reactions to chemotherapy, and 450 μg of granulocyte-colony stimulating factor (G-CSF) was used routinely. The most severe toxicities of all courses of chemotherapy were documented. Adverse events and toxicities were graded according to the National Cancer Institute's common toxicity criteria.[27]

2.3. Dose and schedule modification

Both study arms were subjected to the same protocol dose-reduction criteria according to hematologic or nonhaematologic toxic effects. Full doses of all agents were administered only if the absolute neutrophil count (ANC) was $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. If these levels were not reached, the scheduled treatment was delayed until the counts recovered.

During the double paclitaxel and carboplatin (TC) treatment, the subsequent dose of carboplatin was reduced to AUC = 4–5 for level 1 or 2 hematological toxicity, paclitaxel was reduced to 150 mg/m^2 for level 1 hematological toxicity or to 135 mg/m^2 (for level –2 hematological toxicity). If the platelet count was $< 100 \times 10^9$/L and ANC was $< 1.5 \times 10^9$/L, the treatment cycles were delayed until the recovery of counts. For grades –3/4 hematological toxicities, treatment was administered until recovery and then at 80% of drug dosage. Patients with grade –4 toxicity were withdrawn from the study and treated at the investigator's discretion.

For gemcitabine and other combination agents, full doses of all agents were administered if all target levels were reached. The dose of all drugs was reduced by 20% for patients with grade –3 neurotoxicity and myelosuppression and for grade –IV thrombocytopoenia and hepatotoxicity (bilirubin or persistently elevated transaminases grade 3). During the administration of

gemcitabine on day 8, if the ANC was $< 0.5 \times 10^9$/L or the platelet count was $<50 \times 10^9$/L, the day–8 dose of gemcitabine was omitted.

2.4. Patient evaluation and post-treatment follow-up

Baseline assessment included physical examination (pelvic and neurological examination), complete blood counts (CBC), weights, full biochemical profiles, computed tomography (CT) or ultrasonography, routine urine and stool tests, and chest x-rays. CA-125 was determined before initiating chemotherapy. CBC, CA-125, and liver and kidney function tests were repeated at each cycle. The CBC was to be performed twice weekly if there was documented grade-4 neutropoenia, until it recovered to grade 3. The changes in hematologic and other clinical laboratory tests, physical examination, and the severity of adverse events were documented to evaluate the safety and tolerability of sequential treatment.

After completing all treatment, patients were followed through phone calls, letters, and frequent outpatient visits. Patients were followed for 1 month for 2 years, 3 to 6 months during the third year, and annually thereafter. These time intervals were adjusted at the direction of the attending physician, according to the patient's status. Except for the assessment above, per-abdominal and pelvic computed tomography or magnetic resonance imaging were performed as required.

2.5. Endpoints and statistical analysis

Patients who completed at least one course of therapy were assessed using the World Health Organization response criteria[27] as follows: (1) complete response (CR) was defined as the disappearance of all clinical evidence of tumor plus normalization of the CA 125 level for at least 4 weeks. (2) Partial response (PR) was defined as ≥50% reduction in the sum of the products of the orthogonal diameters of the lesions, which were determined from 2 observations ≤4 weeks apart. (3) Stable disease (SD) was defined as a steady-state response <PR or progression <25% lasting ≥4 weeks. The overall response rate (CR + PR) was estimated as well.

The definition of progression was based on the Response Evaluation Criteria in Solid Tumors criteria and CA125 progression.[28,29] If patients developed 2 simultaneous events, the first documented date was chosen as the date of progression.

This study aimed to evaluate overall survival (OS) and progression-free survival (PFS) and to evaluate the significance of differences between the 2 arms. The primary end point was PFS, and secondary end points were OS and toxicity. OS was defined as the time from the start of treatment to death or the date of the most recent follow-up. PFS was measured from the date of primary cytoreductive surgery to the date of progression or the date of the last follow-up.

The Kaplan–Meier method was used to generate survival curves and to assess PFS and OS rates. The log-rank test and the Cox proportional hazards regression model were used to evaluate the effects of the therapies on OS and PFS. The model included factors with prognostic value such as age, grade, postoperative residuum, neoadjuvant chemotherapy and histology. The chi-square test or Fisher's exact test was used to compare the response rates of the 2 arms. The SPSS statistical software was used to analyze all data. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Patients' and tumor characteristics

Patients' and tumor characteristics are presented in Table 1. We concluded from the data displayed in Table 1 that there were no significant differences between groups in age, postoperative residuum, neoadjuvant chemotherapy, grade, and histology ($P > 0.05$).

3.2. Toxicity

All patients who received at least 1 cycle of chemotherapy were evaluated for toxicity every 2 cycles. We documented hematological toxicity (neutropenia, oligocythemia, thrombocytopinia) and nonhematological (nausea, vomiting, diarrhea, hepatic dysfunction, renal dysfunction, and peripheral neuropathy toxicity) among patients in both different arms. There was no unexpected toxicity associated with either study arm.

3.3. Hematological toxicity

Hematological toxicity was mild, and the major toxicities are listed in Table 2. The predominant hematological toxicities were neutropoenia and thrombocytopoenia as follows: grade III or IV neutropoenia, 33 patients (37.5%) in arm 1; 29 patients (32.2%) in study arm 2. The difference was not significant ($P > 0.05$). Although grade –3/4 hematologic toxicity was observed in almost all patients, myelosuppression was generally short and non-cumulative. No patient required a blood transfusion.

3.4. Nonhematological toxicity

Frequent nonhematological toxicities are listed in Table 3, and the most frequent was neurotoxicity. Peripheral neuropathy occurred in 27.1% and 45.2% of study arms 1 and 2, respectively ($P = 0.026$). There were 13 patients with grade 3/4 febrile neutropoenia in study arm 2, which was temporary, uncomplicated and was most often followed by recovery without sequelae.

Table 1

The cliniopathological parameters between 2 arms.

Patients characteristic	Treatment arm1 (n = 88)	Standard arm2 (n = 90)	P
Median age y, range	55 (21–72)	56 (30–74)	0.60
Postoperative residuum, n (%)			
0 or microscopic	54 (61.4)	43 (47.8)	0.69
≦1cm	47 (38.6)	47 (52.2)	
Neoadjuvant chemotherapy, N (%)			
No	38 (43.2)	41 (45.6)	0.97
One cycle	26 (29.5)	21 (23.3)	
Two cycles	21 (23.9)	25 (27.8)	
≧3 cycles	3 (3.4)	3 (3.3)	
Histology, n (%)			
Serous	41 (46.6)	45 (50.0)	0.97
Mucinous	10 (11.4)	10 (11.1)	
Endometrioid	18 (20.5)	19 (21.1)	
Clear cell	8 (9.1)	7 (7.8)	
Mixed	7 (8.0)	6 (6.7)	
Unknown	4 (4.5)	3 (3.3)	
Grade, n (%)			
Well	4 (4.5)	2 (2.3)	0.724
Moderate	36 (40.9)	37 (42.5)	
Poor	35 (39.8)	33 (37.9)	
Unknown	13 (14.8)	15 (17.2)	

Table 2

Hematological toxicity (WHO grade).

	arm1 (n = 88)					arm2 (n = 90)					
Adverse event	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	***P***
Neutropenia	25	24	14	12	13	19	25	17	14	15	0.85
Oligocythemia	33	21	13	12	9	35	17	14	12	12	0.92
Thrombocytopinia	28	18	22	12	8	27	25	19	10	9	0.81

WHO = World Health Organization.

Table 3

Nonhematological toxicity (WHO grade).

	arm1 (n = 59)					arm2 (n = 62)					
Adverse event	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	***P***
Nausea, vomiting	28	22	15	12	11	35	19	14	10	12	0.876
Diarrhea	47	25	13	3	0	58	20	11	1	0	0.429
Hepatic dysfunction	60	13	13	2	0	66	13	10	1	0	0.722
Renal dysfunction	68	19	1	0	0	66	22	2	0	0	0.742
Peripheral neuropathy	64	14	8	2	0	48	16	13	9	4	0.008

Patients administered sequential therapy did not experience undue or unexpected toxicity. Toxicities such as nausea, vomiting, diarrhea, hepatic dysfunction, renal dysfunction, and peripheral neuropathy were tolerated and did not differ significantly between the 2 study arms (Table 3).

3.5. Response

CRs and PRs were 59.1% and 23.9%, respectively, in study arm 1 and 60% and 26.7%, respectively, in study arm 2. Study arms 1 and 2 achieved 83% and 86.7% CR+PR, respectively, and the differences between the 2 arms were not significantly different (CR, $P = 0.90$; PR, $P = 0.67$ and PR+CR, $P = 0.49$).

3.6. Survival analysis

Survival data were acquired for 88 and 90 patients in study arms 1 and 2, respectively, and the median follow-up was 62 months for both. There was a significant difference in median PFS between groups (study arm 1, 28 months; study arm 2, 19 months; $P = 0.003$) (Fig. 1). There were no significant differences between study arms 1 and 2 in median OS (39 months each), observed1-year OS (92% and 91.1%, respectively) and observed3-year OS (68.2% and 58.9%, respectively) (1-year OS, $P = 0.822$; 3-year OS, $P = 0.198$). The 5-year OS of study arm 1 was significantly longer compared with that of study arm 2 (34.1% vs 18.9%, respectively, $P = 0.021$) (Fig. 2). Analysis using the Cox proportional hazard regression model revealed that PFS and OS were not influenced by age, chemotherapy regimen, neoadjuvant chemotherapy, grade, histology or postoperative residuum (Table 4). Further, when we used multivariable analysis adjusted for covariates, including grade, neoadjuvant chemotherapy, and histology, there were no significant differences.

4. Discussion

We show here that sequential, dual cycles of paclitaxel + carboplatin treatment, followed by gemcitabine-based combina-

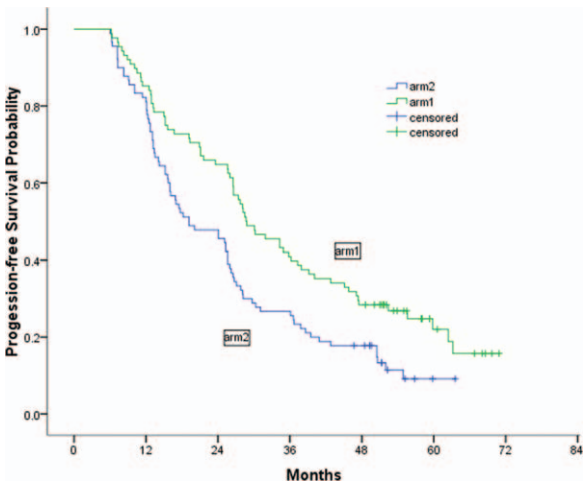

Figure 1. Kaplan–Meier progression-free survival plot by 2 arms. arm1 = paclitaxel–carboplatin followed by gemcitabine-based chemotherapy, arm2 = paclitaxel and carboplatin ($P < 0.01$).

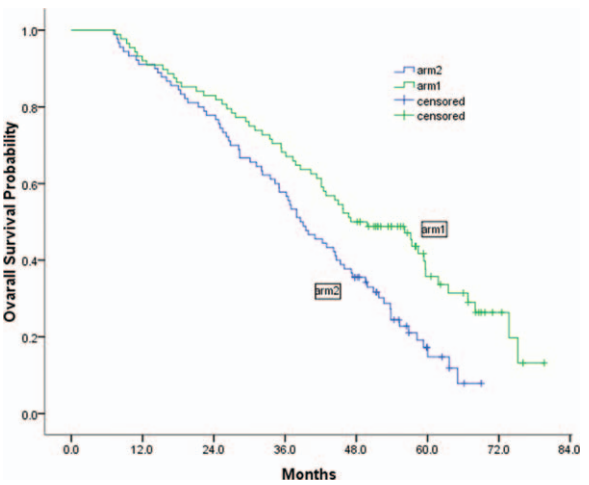

Figure 2. Kaplan–Meier overall survival plot by 2 arms. arm1 = paclitaxel–carboplatin followed by gemcitabine-based chemotherapy, arm2 = paclitaxel and carboplatin ($P < 0.01$).

Table 4

Cox proportional hazard model for PFS and OS.

	PFS		OS	
Factors	**95%CI**	***P***	**95%CI**	***P***
Chemotherapy regimen	1.32–2.62	<0.01	1.29–2.66	<0.01
Age	0.99–1.02	0.64	0.99–1.03	0.34
Grade	0.83–1.25	1.02	0.85–1.31	0.65
Histology	0.81–1.02	0.91	0.90–1.14	0.87
Neoadjuvant chemotherapy	0.99–1.42	0.07	0.94–1.38	0.18
Postoperative residuum	0.66–1.30	0.64	0.54–1.11	0.16

CI = confidence interval, OS = overall survival, PFS = progression-free survival.

tion chemotherapy, were generally effective. The overall response rate in study arm 2 was 86.7%, which is consistent with previous randomized trials reporting overall response rates ranging from 58% to 73%.[5,16,30–32] Here, the overall response rate of study arm 1 (83%) was not significantly different. Further, PFS times differed significantly ($P=0.003$) between study arms 1 (28 months) and 2 (19 months) (follow-up for both arms = 62 months). Possible explanations include the abrogation of emerging drug resistance by the sequential-type approach and the synergism between the cytotoxic effects of the drugs that delayed recurrence. However, there was no difference in 1- and 3-year OS between the 2 study arms, and the 5-year OS of study arm 1 (34.1%) was significantly higher ($P=0.021$) compared with that of study arm 2 (18.0%). We conclude, therefore, that sequentially administering drugs may increase long-term survival.

Despite the combination of carboplatin and paclitaxel as the standard treatment for ovarian cancer, many patients relapse, and approximately two-thirds die after 5 years.[33] Numerous published studies aimed to further improve therapy. For example, Hansen et al[34] first proposed that gemcitabine could be incorporated into first-line therapy of ovarian cancer, and although they achieved a 100% response rate (n = 24), the patients experienced a high rate of hematological toxicity.

Sequential chemotherapy is widely used to treat breast cancer[35,36] and nonsmall cell lung cancer,[37,38] and is highly active in patients with acceptable levels of toxicity. However, the efficacy of sequential chemotherapy is not established for ovarian cancer. Therefore, we administered all drugs sequentially to eliminate severe hematologic toxicities and to achieve high response rates, which were addressed using the triplet combination with encouraging outcomes.

Diverse randomized trials are investigating sequential chemotherapy as first-line treatment for ovarian cancer to further improve patients' outcomes;[20,39–43] however, the results are inconsistent. For example, Steer et al[42] enrolled 20 patients with epithelial ovarian cancer (FIGO III–IV) and administered a sequential double regimen comprising gemcitabine and oxaliplatin before 4 cycles of carboplatin and paclitaxel that achieved an 85% overall response rate, but with unacceptable neurotoxicity. Friedlander[20] et al treated 47 patients (previously untreated) with advanced ovarian cancer with sequential carboplatin followed by combined gemcitabine–paclitaxel. In this study, myelosuppression was the predominant toxicity, the frequencies of grades –3 and –4 neutropenic toxicities and thrombocytopoenia were 76.6% and 12.8%, respectively. There was no significant difference in outcomes of the 2 study arms. Brotto et al evaluated the difference between a sequential approach using cisplatin-topotecan followed by carboplatin–paclitaxel and paclitaxel–carboplatin. The quality of life of the sequential arm was not superior to that of the standard arm. However, in our study, short-lasting and manageable myelotoxicity was observed in the 2 study arms as follows: 33 patients (37.5%) had grade –III or –IV neutropenic toxicity in study arm 1 and 29 patients (32.2%) in study arm 2, and the differences were not statistically different. Neurotoxicity affected 45.2% of subjects in study arm 2, which was significantly higher compared with 27.1% of subjects in study arm 1, indicating that our approach was generally well tolerated.

Hoskins et al[41] applied 4 sequential cycles of cisplatin/topotecan followed by 4 cycles of paclitaxel/cisplatin. This phase II study (n = 34) achieved a 78% overall response rate, and the elevated CA125 levels returned to normal in 30/39 (77%) patients. Their phase III study[39] did not show promise, because there was no significant difference between the median PFS in the treatment (14.6 months) and reference (16.2 months) groups. However, in the study of Friedlander et al[20] in which all patients underwent initial surgery or biopsy, median PFS was 13.8 months (median follow-up, 31.2 months), OS was 31.2 months, and 1- and 3-year OS rates were 95.7% and 44.2%, respectively. They concluded that the sequential approach is a feasible first-line treatment, which is consistent with our present findings.

The differences between the present and published studies may be explained by the mechanism of action of the sequentially administered drugs of choice. The combination of carboplatin with paclitaxel is considered the gold treatment for ovarian cancer, and it is therefore reasonable to use this combination for first-line treatment. Further, killing chemoresistant cells requires drugs with distinct cytotoxic mechanisms. It is therefore disappointing that topotecan may not serve as a suitable candidate.[39,44,45]

We used gemcitabine because of its encouraging effectiveness for treating pretreated or untreated patients with ovarian cancer as well as its suggested ability to overcome resistance to platinum.[14,46–49] Further, more than 3 to 4 cycles of platinum-based chemotherapy does not improve their efficacy for treating non-small cell lung cancer.[50,51] Thus, further platinum-based treatment did not increase the response rates and OS, but caused overlapping toxicity.[50,51] Accordingly, we changed gemcitabine-based combination chemotherapy after four cycles of paclitaxel/carboplatin without causing severe toxicity. Moreover, our routine use of G-CSF most likely reduced toxicity.

Another potential explanation of the differences between studies is the nonrational application order of the drugs, which act through diverse mechanisms as described above. Combining all drugs to develop an effective approach is advantageous for reducing significant overlaps in toxicity as we show here. For

example, Poole[52] et al found that paclitaxel followed by gemcitabine may achieve additive or synergistic antitumour activity if the dose of gemcitabine is sufficient, and increased toxicity was not observed. Similarly, the opposite sequence may generate antagonistic effects. We show here, for the first time to our knowledge, that there was no long-lasting and cumulative toxicity induced by a sequential regimen that did not include a taxane or platinum compound.

The response to further platinum-based treatment for patients with recurrent disease depends on their response to such therapy before and during the platinum-free interval (PFT).[53] The study cited reports a response rate of 59% for patients with a PFT >2, which is 27% higher in patients with a PFT <1 year.[53] We show here that PFS differed between the 2 study arms, although the difference between 1- and 3-year OS was not significantly different. However, the 5-year OS of study arm 1 was significantly higher compared with that of study arm 2 (34.1% vs 18% respectively, $P=0.021$). Our sequential approach to treatment using paclitaxel and carboplatin followed by nontaxane- and nonplatinum-based drugs may contribute to improving PFT and enhance the effects of paclitaxel and platinum.

There are limitations to our study as follows: (1) the prognosis of our patients (FIGO IIIc) was poor. Therefore, the effects of our sequential approach on patients with other stages require further study. (2) The follow-up was relatively short. (3) A study of a larger patient population will be required to support our findings.

5. Conclusion

In summary, the use of 4 cycles of paclitaxel and carboplatin followed by 2 to 4 cycles of a gemcitabine-based combination (GEM+IFO+/–ADM/EPI) was an active and tolerable treatment approach. These promising findings justify further research to support the implementation of this regimen as first-line therapy required improve the otherwise dismal outcomes of patients with advanced ovarian cancer.

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