Paclitaxel plus nedaplatin vs. paclitaxel plus carboplatin in women with epithelial ovarian cancer: A multi-center, randomized, open-label, phase III trial

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Abstract. The multi-center, randomized, open-label, phase III trial discussed in the present study was performed to compare the clinical outcomes of nedaplatin (NDP) plus paclitaxel, and carboplatin (CBP) plus paclitaxel for the treatment of epithelial ovarian cancer (EOC). In the current study, 182 patients with International Federation of Gynecology and Obstetrics (FIGO) stage II-IV EOC were randomly assigned to receive NDP plus paclitaxel or CBP plus paclitaxel at 3-week intervals for a total of six courses. The primary endpoints were progression-free survival rate (PFS) and overall survival rate (OS). The secondary endpoints were toxicity profiles. The median follow-up was 44.63 months [95% confidence interval (CI) 33.67-46.47 months] for the NDP group and 47.63 months (95% CI 45.13-49.07 months) for the CBP group. Overall, there was no significant difference in PFS or OS between the two groups (P=0.09 for PFS, and P=0.65 for OS). For the patients with FIGO stage III-IV EOC, the NDP plus paclitaxel regimen significantly prolonged PFS (P=0.02) but did not result in improved OS (P=0.53) when compared with the CBP group. The patients in the NDP plus paclitaxel group also exhibited a lower incidence rate of grade 3 or 4 leucopenia (P=0.03). Other hematological and non-hematological toxicity profiles were similar between the two groups. Compared with CBP plus paclitaxel regimens, NDP plus paclitaxel regimens achieved comparable survival outcomes and similar toxicity profiles. However, patients of FIGO stage III-IV EOC may experience more clinical benefits from NDP plus paclitaxel treatment, including a prolonged PFS and a lower incidence rate of leucopenia. Therefore, an NDP-based regimen may be an alternative choice when using platinum-based agents to treat EOC.

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Introduction

Epithelial ovarian cancer (EOC) is one of the three most common malignant tumors of the female reproductive system (1). Owing to the lack of early diagnosis modalities

and effective treatment measures, >70% of the patients are diagnosed at an advanced disease stage, and this is associated with high rates of morbidity and mortality (2). At present, the standard therapy for advanced ovarian cancer usually includes primary surgical cytoreduction and chemotherapy (3,4). The two-drug combination of paclitaxel and carboplatin (CBP) is considered the standard first-line chemotherapy for patients with EOC (5). Although this standard chemotherapy initially yields a high response rate (>80%), >70% of women with advanced-stage EOC experience recurrence within 5 years and develop drug resistance (2,6). This regimen has been associated with serious adverse effects including myelosuppression, alopecia, neurotoxicity and fatigue, which affect the tolerance of patients to the therapy, and their quality of life. Therefore, it is necessary to search for chemotherapy regimens with superior safety and efficacy for the treatment of EOC.

Nedaplatin, namely 254-S, NDP (cisplatin analogue), is a second-generation platinum derivative developed by Shionogi & Co., Ltd. (Osaka, Japan). Experiments *in vitro* demonstrated that NDP inhibited tumor cell proliferation in human cervical and ovarian cancer (7,8). *In vivo*, NDP exhibited an antitumor effect in tumor-bearing animals (9,10). Results of phase II studies in Japan revealed that NDP exerted pronounced antitumor activity against various solid tumors, including lung, esophageal, head and neck, testicular, and cervical cancer, and ovarian carcinoma (11-16). Response rates of at least 25% have been achieved with 100 mg/m^2 NDP monotherapy in a range of different types of cancer (17). The response rate to NDP monotherapy was 38 and 34-46% in ovarian and cervical cancer, respectively (11,13). Furthermore, NDP has been reported to exhibit higher antitumor activity in cervical cancer compared with CBP (18,19).

On the basis of the above results, a multi-center, randomized, open-label phase III trial was designed to compare the clinical outcomes of NDP plus paclitaxel and CBP plus paclitaxel in the treatment of epithelial ovarian cancer. The trial was designed to test whether the efficacy and tolerability of NDP was maintained in combination with paclitaxel. The endpoints, including progression-free survival (PFS), overall survival (OS), and toxicity profiles, were compared between the two groups to provide further evidence for the clinical application of NDP.

Patients and methods

Patients. A total of 182 patients with epithelial ovarian cancer [International Federation of Gynecology and Obstetrics (FIGO) stage II-IV] (20) were enrolled between August 2010 and April 2012 at 14 centers (Cancer Hospital of Guangxi Medical University, Nanning; Tongji Hospital, Shanghai; West China Second University Hospital, Chengdu; Shanghai General Hospital, Shanghai; Peking University First Hospital, Beijing; Women's Hospital School of Medicine Zhejiang University, Hangzhou; Qilu Hospital of Shandong University, Jinan; Daping Hospital, Research Institute of Surgery Third Military Medical University, Chongqing; Jiangsu Cancer Hospital, Nanjing; The First Affiliated Hospital of Haerbin Medical University, Haerbin; Chongqing Cancer Hospital, Chongqing; Cancer Hospital Chinese Academy of Medical Science, Beijing; The Second Affiliated Hospital of Tsinghua University, Beijing; Peking University People's Hospital, Beijing), in China. Clinicopathological characteristics are presented in Table I. A computer-based minimization procedure was used to randomly allocate participants at a 1:1 ratio to either the standard schedule of CBP plus paclitaxel or the experimental schedule of NDP plus paclitaxel. The procedure of centralized randomization was conducted by the Department of Biostatistics, Nanjing Medical University (Nanjing, China). The ethics committee of each participating center approved the study protocol. Written informed consent was obtained from every participant prior to enrolment and randomization. The main inclusion criteria were as follows: i) Patients had pathologically or cytologically confirmed epithelial ovarian cancer [The International Federation of Gynecology and Obstetrics (FIGO) stage II-IV] followed by optimal cytoreductive surgery; ii) patients were aged between 18 and 70 years old; and iii) patients exhibited adequate hematological, renal, and hepatic function. In addition, all included patients had no other serious medical problems, and no intracranial or bone metastases. Good adherence, regular follow-up and voluntary compliance with the provisions of this research were required. Patients were excluded it they failed to complete the planned cycles because of progressive disease or any other reason. Patients who were pregnant or lactating were also excluded from the present study. The trial was registered with the Chinese Clinical Trial Registry (no. ChiCTR-TRC-11001333).

Therapeutic regimens. All drugs were obtained from Jiangsu Aosaikang Pharmaceutical Co., Ltd. (Nanjing, China). Patients assigned to the experimental group (NDP group) received paclitaxel (175 mg/m^2) plus NDP (80 mg/m^2) whereas patients in the control group (CBP group) received paclitaxel (175 mg/m^2) plus CBP [area under the curve (AUC) 5 mg/ml per min according to the Calvert formula] (21). Creatinine clearance was estimated according to the Cockcroft-Gault formula (22). The treatment was administered once every 3 weeks for a total of six cycles. NDP was dissolved in 500 ml of normal saline prior to use and infused over 2 h. To avoid kidney damage, particularly in patients producing <1,500 ml urine per 24-h, >1,000 ml intravenous infusion of paclitaxel (80 mg/m^2) plus NDP (80 mg/m^2) was administered following administration of NDP. Paclitaxel was diluted in 500 ml 5% glucose diluted in hydrochloric acid water prior to intravenous drip administration for at least 3 h. To prevent paclitaxel-associated allergic reactions, the patients were orally pre-medicated with 10 mg dexamethasone 12 h prior to paclitaxel infusion and 30 min prior to paclitaxel infusion with 10 mg dexamethasone by intravenous injection, 400 mg diphenhydramine by intravenous infusion and 20 mg cimetidine by intramuscular injection. CBP was infused intravenously in 500 ml 5% glucose diluted in hydrochloric acid water over 2 h. To assess the risk of acute toxic effects, hematological measurements were performed at every administration of chemotherapy. An absolute neutrophil count of >1.5x10^9 cells/l, a white blood cell count of >3.0x10^9 cells/l and a platelet count of >100x10^9 cells/l at the beginning of treatment were required for patients; otherwise, treatment was delayed until the required hematological counts were achieved. Treatment delay was permitted because pronounced toxic effects in patients require a treatment discontinuation of 2 weeks or longer. In the two study groups,

Table I. Patient characteristics.

Characteristic	NDP group	CBP group	P-value
Age, years	50.82±9.83[a]	50.84±10.30[a]	0.98
FIGO stage, n (%)			
II	28 (30.77)	19 (21.11)	0.66
III	52 (57.14)	67 (74.44)	
IV	12 (12.09)	4 (4.44)	
Treatment status, n (%)			
Initial treatment	86 (93.48)	86 (95.56)	0.75
Retreatment	6 (6.52)	4 (4.44)	
Marital status, n (%)			
Married	91 (98.91)	86 (95.56)	0.21
Unmarried	1 (1.09)	4 (4.44)	
Background disease, n (%)			
No	76 (82.61)	76 (84.44)	0.84
Yes	16 (17.39)	14 (15.56)	
Operation, n (%)			
No	42 (45.65)	42 (46.67)	1.00
Yes	50 (54.35)	48 (53.33)	
Radiotherapy, n (%)			
No	92 (100.00)	90 (100.00)	-
Yes	0 (0.00)	0 (0.00)	
Chemotherapy, n (%)			
No	73 (79.35)	71 (78.89)	1.00
Yes	19 (20.65)	19 (21.11)	
Biotherapy, n (%)			
No	92 (100.00)	90 (100.00)	-
Yes	0 (0.00)	0 (0.00)	
History of drug allergy, n (%)			
No	85 (92.39)	86 (95.56)	0.54
Yes	7 (7.61)	4 (4.44)	
Pathological/cytological patterns, n (%)			
Serous adenocarcinoma	57 (62.64)	58 (65.17)	0.53
Mucinous adenocarcinoma	7 (7.69)	4 (4.49)	
Clear-cell carcinoma	7 (7.69)	3 (3.37)	
Endometrioid adenocarcinoma	7 (7.69)	11 (12.36)	
Other	14 (14.29)	14 (14.61)	
ECOG score, n (%)			
0	69 (75.00)	60 (66.67)	0.19
1	23 (25.00)	28 (31.11)	
2	0 (0.00)	2 (2.22)	
Treatment cycles, n (%)			
1	8 (8.70)	3 (3.33)	0.07
2	5 (5.43)	4 (4.44)	
3	0 (0.00)	1 (1.11)	
4	10 (10.87)	8 (8.89)	
5	10 (10.87)	5 (5.56)	
6	59 (64.13)	69 (76.67)	

[a]Data are presented as the mean ± standard deviation. NDP, nedaplatin plus paclitaxel regimen; CBP, carboplatin plus paclitaxel regimen; FIGO, International Federation of Gynecology and Obstetrics. ECOG, Eastern Cooperative Oncology Group.

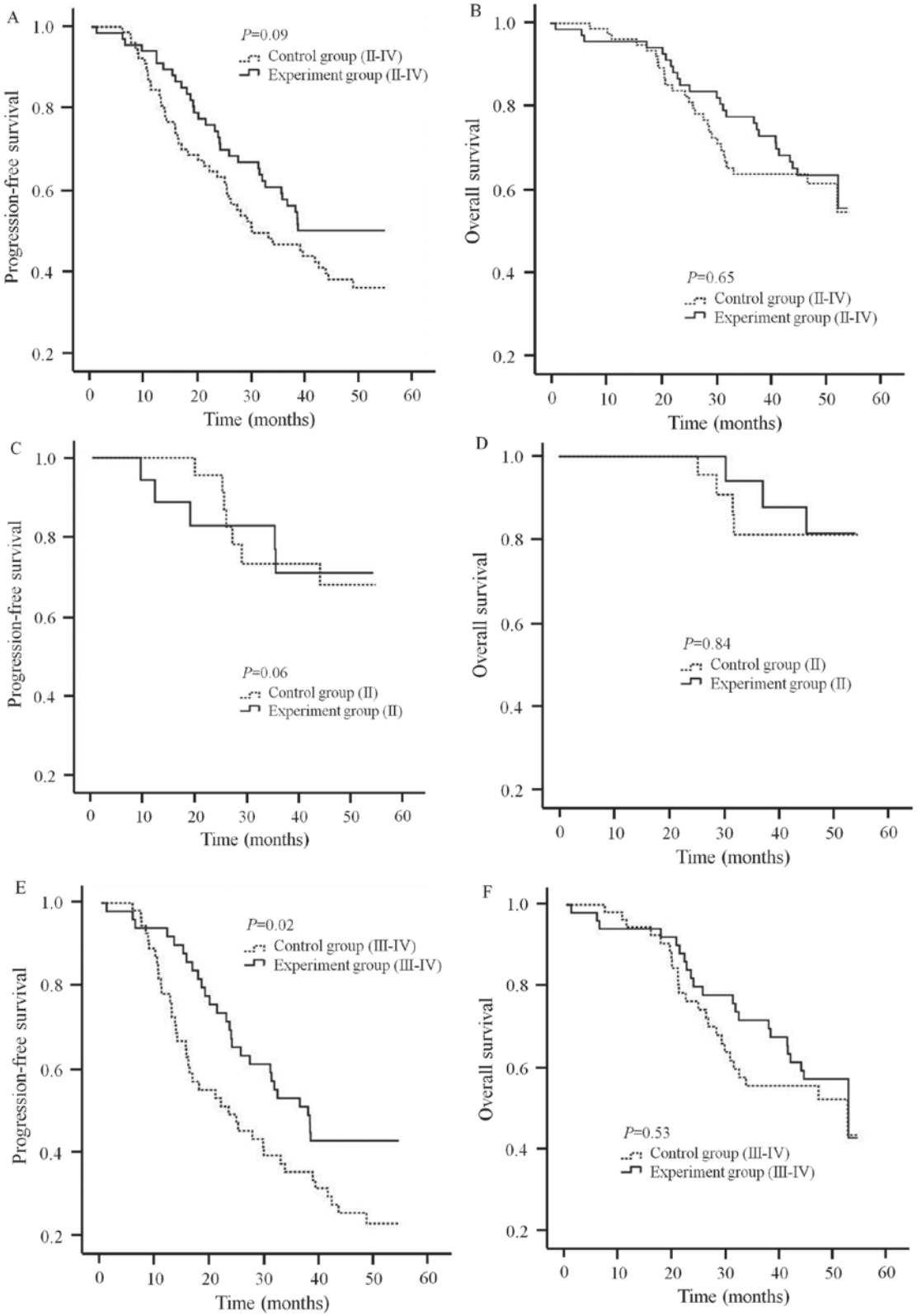

Figure 1. Kaplan-Meier analysis of PFS and OS rate in patients with advanced epithelial ovarian cancer, categorized by treatment schedule. Comparisons were performed using the log-rank test. (A) PFS and (B) OS of all patients in the control (carboplatin plus paclitaxel) and experimental (nedaplatin plus paclitaxel) groups. (C) PFS and (D) OS of the patients with FIGO stage II ovarian cancer. (E) PFS and (F) OS of the patients with FIGO stage III-IV ovarian cancer. PFS, progression-free survival; OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics.

the doses of all drugs were reduced by 20% if the neutrophil count fell to $<0.5x10^9$ cells/l or platelet count to $<50x10^9$ cells/l for 7 days or longer. The drug doses were reduced by 25% if grade 2 neuropathy arose. Chemotherapy was continued until unacceptable toxicity was observed, or the patient refused further treatment.

Table II. Comparison of adverse reactions between the two groups.

		Classification of adverse reaction									
Symptom	Group	0	I	II	III	IV	Total	Incidence (%)	P-value	Grade III-IV incidence (%)	P-value
Leukocyte	NDP	16	30	36	9	1	92	82.61	0.69	10.87	0.03
	CBP	13	24	32	20	1	90	85.56		23.33	
Thrombocyte	NDP	58	21	8	5	0	92	36.96	0.37	5.43	0.28
	CBP	50	21	10	9	0	90	44.44		10.00	
Granulocyte	NDP	22	25	22	16	7	92	76.09	0.47	25.00	0.08
	CBP	17	11	28	19	15	90	81.11		37.78	
Hemoglobin	NDP	14	27	43	8	0	92	84.78	1.00	8.70	0.63
	CBP	14	29	37	8	2	90	84.44		11.11	
TBIL	NDP	87	0	5	0	0	92	5.43	0.77	0	0.50
	CBP	84	0	5	1	0	90	6.67		1.11	
Creatinine	NDP	89	3	0	0	0	92	3.26	0.25	0	-
	CBP	90	0	0	0	0	90	0		0	
ALT	NDP	60	31	1	0	0	92	34.78	1.00	0	-
	CBP	59	30	1	0	0	90	34.44		0	
AST	NDP	67	25	0	0	0	92	27.17	0.39	0	-
	CBP	71	19	0	0	0	90	21.11		0	
Nausea/vomiting	NDP	24	48	17	3	0	92	73.91	0.51	3.26	0.50
	CBP	28	38	19	4	1	90	68.89		5.56	
Peripheral nervous system	NDP	71	17	4	0	0	92	22.83	1.00	0	-
	CBP	69	19	2	0	0	90	23.33		0	

NDP, nedaplatin plus paclitaxel regimen; CBP, carboplatin plus paclitaxel regimen; TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate transaminase.

Evaluation indicators and statistical analysis. The primary objective of the present study was to compare PFS and OS between the two treatment groups. Secondary endpoints were toxicity profiles. PFS was defined as the interval between the first day of randomization and date of first relapse, progression or death (whichever occurred first) or the date of the last follow-up for patients alive at the end of the study without progression. Surviving patients or patients lost to follow-up were censored at the date last known to be alive. Descriptive data were presented as frequencies and percentages. Patient characteristics in the two groups were compared using Pearson's χ^2 test. Differences in OS and PFS were calculated using Kaplan-Meier curves and compared using the log-rank test. All P-values were two-tailed and $P<0.05$ was considered to indicate a statistically significant difference. All analyses were conducted by independent third-party statisticians from the Department of Biostatistics, Nanjing Medical University, using SPSS 19.0 software (IBM Corp, Armonk, NY, USA).

Results

Characteristics of patients. The randomized, multi-center, open-label, phase III trial analyzed 182 patients with EOC between August 2010 and April 2012. Of these patients, 92 received NDP plus paclitaxel regimens and 90 received CBP plus paclitaxel regimens. The patient characteristics are presented in Table I. No statistical difference was observed between the two groups with regard to age, FIGO stage, initial treatment or retreatment, marital status, background disease or complications, history of drug allergies, pathological patterns or Eastern Cooperative Oncology Group score (23). All enrolled patients received between 1 and 6 cycles of chemotherapy. The chemotherapy duration was 5.02±1.63 [mean ± standard deviation (SD)] cycles in the NDP group and 5.39±1.30 (mean ± SD) cycles in the CBP group (P=0.07; Table I). A number of patients received surgery, radiotherapy, chemotherapy, biotherapy or other treatments prior to the trial, but there was no statistical difference between the two groups (Table I).

Response to treatment and survival. In the present study, the date of last the follow-up was May 20, 2015. A small proportion of the patients (35/182) were lost to the follow-up due to loss of contact, and their data were thus excluded from the survival analysis. There was no statistically significant difference in censoring or lost-to-follow up status between the two groups (data not shown). The median follow-up times for the NDP group and CBP group were 44.63 months [95% confidence interval (CI): 33.67-46.47 months] and 47.63 months (95% CI: 45.13-49.07 months), respectively.

With respect to the primary endpoints, the difference in the 5-year OS or PFS rate was not significant between the NDP and the CBP groups. The PFS rate in the NDP group (50.20%) was not statistically different from that of the CBP group (36.20%; Fig. 1A; P=0.09), as revealed by Kaplan-Meier analysis. Similarly, the 5-year OS rate was 63.5% in the NDP group and 61.5% in the CBP group. Although the NDP group exhibited a higher OS rate than the CBP group, no statistical difference was observed between the two groups (Table II and Fig. 1B; P=0.65). Thus, the two treatment groups had the same effect in terms of prolonging the lifespan of patients, and delaying the progression of EOC.

Stratification analysis was further performed according to FIGO stage. For patients with FIGO II stage EOC, the PFS and OS were not statistically different between the NDP group and the CBP group (P=0.06 for PFS, P=0.84 for OS; Fig. 1C and D). For the patients with FIGO stage III-IV EOC, the OS rate in the two groups did not significantly differ (Fig. 1F; P=0.53). However, the PFS rate in the NDP group was significantly higher than the CBP group (Fig. 1E; P=0.02).

Toxicity profiles. With respect to the secondary endpoints, the hematological and non-hematological toxicity profiles were summarized in Table II. A significant difference was observed in the white blood cell count and occurrence of grade 3 or 4 leucopenia between the two groups. The incidence of leucopenia was higher in the CBP group than the NDP group (23.33 vs. 10.87%; P<0.05). The rate of granulopenia, thrombocytopenia, hemoglobinemia and nausea/vomiting tended to be lower in the NDP group when compared with the CBP group; however, no statistical difference was observed between the two groups. Furthermore, no grade 3 or 4 renal toxicity or neurotoxicity was observed in the two groups.

Discussion

EOC is the most lethal gynecological malignancy and is sensitive to chemotherapy. Survival is markedly improved when a combination of paclitaxel and platinum-based chemotherapy is administered as a first-line therapy. Even so, the rates of recurrence and mortality remain high (24,25). Thus, improved treatments for this disease are required. One option is to substitute NDP for CBP, as has been done in the present study. The present phase III trial intended to compare the clinical efficacy of the experimental regimen of NDP plus paclitaxel and the control regimen of CBP plus paclitaxel as first-line treatments for patients with EOC.

According to previous studies, the median PFS time was 16-21 months and the median OS time was 32-57 months in patients with advanced EOC (26-30). In the present study, the observed PFS time was longer (38.23 months for the NDP group and 29.80 months for the CBP group), while the observed OS time was similar to the value previously reported (55.63 months for the NDP group and 55.10 months for the CBP group). The results of the present study indicated that prolonged PFS did not result in longer OS, a result also indicated in previous studies (30,31).

Overall, there was no statistical difference in PFS and OS between the two groups. However, stratified analysis revealed that that the NDP treatment significantly extended PFS time of patients with FIGO stage III-IV EOC (37.90 compared with 23.33 months; P=0.02). The observed survival benefits of NDP may be explained by increased compliance and the greater number of chemotherapy cycles that the patients received. Markman *et al* (32) reported that the incidence of hypersensitivity reactions (HSRs) against CBP increased with repeated treatment. In the present study, the patients who received NDP suffered less from leucopenia (Table II). It was also reported that NDP was less renally toxic and had relatively lower rate of neurotoxicity (33). Michikami *et al* (34) revealed that the substitution of NDP for CBP allowed for continued administration of platinum agents, hence the patients who were treated with NDP may complete more chemotherapy cycles than those treated with CBP.

In conclusion, the present multi-center, randomized, open-label phase III trial indicated that NDP-based regimens may be alternative platinum-based treatments for EOC. Compared with CBP plus paclitaxel regimens, NDP plus paclitaxel regimens achieved comparable survival outcomes and similar toxicity profiles. However, patients with FIGO stage III-IV disease may experience more clinical benefits, including prolonged PFS and a lower incidence rate of leucopenia, from NDP plus paclitaxel treatment.

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