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Original Article

Olaparib and paclitaxel in combination with carboplatin in treatment of ovarian cancer: influence on disease control

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Abstract: Objective: To investigate the efficacy and safety of olaparib and paclitaxel combined with carboplatin in the treatment of ovarian cancer and its impact on disease control. Methods: The medical data of 120 patients with ovarian cancer admitted to our hospital from February 2019 to February 2020 were retrospectively analyzed. According to different treatment methods, the enrolled patients were divided into two groups: a control group (n=60) treated with paclitaxel combined with carboplatin, and an experimental group (n=60) additionally treated with olaparib on the basis of the control group. The short-term efficacy, serum levels of carbohydrate antigen 125 (CA125), tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and human epididymis protein 4 (HE4), and the incidence of adverse effects and tumor metastasis were compared between the two groups. Results: There was no difference in the baseline data between the two groups (P>0.05). The objective remission rate (ORR) and disease control rate (DCR) of the experimental group were higher than those of the control group (P<0.05). The experimental group had lower levels of serum CA125, TNF-α, IL-6, and HE4 than the control group after treatment (P<0.05). The two groups showed no significant difference in the incidence of adverse reactions (P>0.05). The one-year follow-up identified a lower tumor metastasis rate in the experimental group compared to the control group (P<0.05). Conclusion: Olaparib and paclitaxel combined with carboplatin improve the serum indexes of patients with ovarian cancer, enhance the disease control, and reduce the recurrence rate, without extra toxic side effects.

Keywords: Olaparib, paclitaxel, carboplatin, ovarian cancer

Introduction

Ovarian cancer is a common clinical gynecologic malignant tumor, to which middle-aged and elderly women during menopause are susceptible. Its mortality ranks first among gynecologic malignant tumors, with more than 200,000 new cases of ovarian cancer recorded each year worldwide, accounting for 13.3% of total cases of gynecologic malignant tumors [1-3]. Due to the special ovarian structure and small tumor size, the early diagnostic yield of ovarian cancer in clinical practice is far from satisfactory, with 50.0%-71.0% of patients in the middle and advanced stages at the time of diagnosis [4], which leads to increased treatment difficulty. Surgery combined with chemotherapy is currently considered the optimal treatment for ovarian cancer, and the efficiency of platinum-based chemotherapy can reach up to 80.0% [5, 6]. Moreover, platinum drugs can act synergistically with paclitaxel to further improve the efficacy and reduce the incidence of adverse effects. Nevertheless, recurrence after 1-2 years of platinum-based therapy has been reported in over 70.0% of patients with ovarian cancer [7], which entails the combination of other therapeutic measures. Currently, patients with recurrent ovarian cancer are classified into platinum-sensitive and platinum-resistant types according to their sensitivity to platinum drugs [8]. However, most platinum-sensitive cases are still treated with platinum-based chemotherapy. To the best of our knowledge, long-term chemotherapy will shorten efficacy duration, and transform the platinum-sensitive patients into resistant ones, not sensitive to drugs [9].

Combination chemotherapy regimens are effective in improving efficacy and reducing the incidence of adverse effects. Paclitaxel is a natural antitumor plant-like drug that acts specifically in the G2 and M phases of cells, preventing microtubules from forming spindle bodies and spindle filaments during mitosis to block the division and multiplication of tumor cells [4]. Carboplatin is a second-generation platinum anticancer drug among cell cycle nonspecific drugs that mainly induces cross-linking of DNA in target cells, impedes DNA synthesis, and prevents DNA replication, thereby inhibiting the growth of tumor cells, with mild gastrointestinal reactions, almost no hearing loss, low neurotoxicity, and dose-limiting toxicity of reversible myelosuppression. The combination of paclitaxel and carboplatin can synergistically act on different tumor cell targets and temporal phases. A high objective efficacy, high quality of life of patients, and mild toxic effects of paclitaxel in combination with carboplatin in the treatment of recurrent ovarian cancer are much preferred in clinical application, and joint treatment with hormones, gene, or targeted therapy may further potentiate the efficacy. Therefore, relevant guidelines in 2016 recommended maintenance therapy with poly ADP-ribose polymerase (PARP) inhibitors in patients with platinum-sensitive ovarian cancer [10], of which olaparib is an example. Olaparib, a potent oral PARP inhibitor, is highly effective in enhancing disease-free survival, delaying disease progression, and lowering the risk of death in patients with ovarian cancer. Nevertheless, there is little research on the treatment of ovarian cancer with olaparib and paclitaxel in combination with carboplatin.

Accordingly, this study investigated the efficacy and safety of the combination therapy for ovarian cancer. The novelty of this study is that a combination of multiple drugs can reduce adverse chemotherapy reactions, lower the recurrence rate, and prolong survival. This may provide new therapeutic insight into clinical treatment.

Materials and methods

Baseline information

This retrospective study was conducted using medical data of patients with ovarian cancer admitted to our hospital from February 2019 to February 2020. The study participants were 120 patients with ovarian cancer who were divided equally into an experimental group (n=60) and a control group (n=60) according to different treatment methods. After recruitment, the patients were informed of the purpose, significance, content, and confidentiality of the study by the research team and signed an informed consent form. This study was approved by the hospital ethics review committee, with an approval number of 2019-01-28. This study was conducted in compliance with the principles laid down in *the Declaration of Helsinki* [14].

Patients were included according to the following criteria: (1) a confirmed diagnosis of ovarian cancer by histological examination or cytology [11]; (2) being treated in our hospital throughout the whole study, without death, hospital referral, or discontinuation of treatment; (3) normal organ function within 28 d before treatment, and no abnormalities as indicated by electrocardiogram and chest X-ray; (4) an expected survival of ≥ 6 months; (5) a Carlsbad score of ≥ 65 points [12]; (6) tumor stage II-IV according to the International Federation of Gynecology and Obstetrics (FIGO) staging [13]. In contrast, patients who met any of the following criteria were excluded: (1) hearing impairment, language impairment, unconsciousness, or mental illness that prevents normal communication; (2) withdrawals, or loss to follow-ups, death, or changed treatment regimen; (3) poor physical constitution that could not tolerate chemotherapy; (4) other serious organic diseases, such as malignant tumors and liver and kidney insufficiency; (5) coagulation dysfunction; (6) history of radiotherapy; (7) severe abdominal adhesions.

Methods

All patients were treated with paclitaxel combined with carboplatin, as well as a routine diuretic, hydration, and antiemetic therapies before treatment. On the first day, 135-175 mg/m^2 paclitaxel (Yangtze River Pharmaceutical Group Co., Ltd., NMPA Approval Number H20058719) was diluted into 500 mL 5% dextrose for intravenous infusion. On the second day, 350-400 mg/m^2 of carboplatin (Yangtze River Pharmaceutical Group Jiangsu Hai Ci Biological Pharmaceutical Co., Ltd., NMPA Approval

Number H20065621) was diluted into 1000 mL 5% glucose and delivered by intraperitoneal infusion. Thirty minutes before chemotherapy, 10 mg diazepam injection (TonghuaMaoxiang Pharmaceutical Co., Ltd., NMPA Approval Number H22022683) was administered intramuscularly, followed by the intravenous dripping of 10 mg dexamethasone injection (Tianjin Tianyao Pharmaceutical Co., Ltd., NMPA Approval Number H20033553) 10 minutes later. After another 10 minutes, 4 mg tropisetron hydrochloride injection (Jiangsu Hengrui Pharmaceutical Co., Ltd., NMPA Approval Number H20061193) was administered intravenously to prevent allergic reactions. Patients' vital signs and indicators were closely monitored during chemotherapy. All patients received two 3-week chemotherapy courses with an interval of 3 weeks.

The experimental group was additionally treated with olaparib. Within 4 weeks after the last chemotherapy, patients received olaparib treatment (AstraZeneca, NMPA Approval Number H20180048) at a starting dose of 300 mg twice a day. Administered at the same time each day, the drug was taken with a glass of water without chewing, crushing, dissolving, or breaking the drugs, with a 12-hour interval between doses. For patients who vomited after administration, this dose was replenished only if the vomited tablets were visibly intact. Olaparib was administered for 2 months.

Outcome measures

Primary outcome

Short-term efficacy: Treatment efficacy was evaluated according to the Response Evaluation Criteria In Solid Tumors (WTO 2000) at 1 month after treatment [15]. Complete response (CR): The lesion disappeared completely, and remission was maintained for more than 1 month, with no new lesions and normal level of tumor markers. Partial response (PR): The sum of the maximum diameter of the target lesions was reduced by >30%, which lasted for more than 1 month. Stable disease (SD): The sum of the maximum diameter of the target lesions was reduced by ≤ 30%, or increased by ≤ 20%. Progressive disease (PD): The sum of the maximum diameter of the target lesions increased by ≥ 20%, or new lesions appeared. Objective response rate (ORR)=CR+PR, and disease control rate (DCR)=CR+PR+SD. The treatment efficacy in the two groups was compared.

Incidence of adverse reactions: The adverse reactions recorded in this study included leukopenia, decreased hemoglobin, impaired liver and kidney function, nausea and vomiting, thrombopenia, hair loss, peripheral neuritis, anemia, and chest tightness. The number of patients with adverse reactions after olaparib treatment was counted.

Tumor metastasis: Patients were followed up regularly for 1 year, and tumor metastasis was examined by positron emission tomography-computed tomography (PET-CT) after olaparib treatment.

Secondary outcome

General information: The general information, including the number of hospitalizations, name, age, weight, body mass index (BMI), FIGO staging, pathologic types, place of residence, monthly income, marital status, and education level, were compared between the two groups.

Serum carbohydrate antigen 125 (CA125), tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and human epididymis protein 4 (HE4) levels: Morning fasting venous blood was collected from patients before treatment (T1) and at 1 (T2) and 2 (T3) months after olaparib administration and centrifuged at 3000 r/min for 5 min to obtain the serum. Serum CA125, TNF-α, IL-6, and HE4 levels were determined using the enzyme-linked immunosorbent assay (Beijing Kewei Clinical Diagnostic Reagent Co., Ltd., NMPA Approval Number S20060028).

Statistical analyses

Statistical analysis was processed by SPSS 20.0 software (IBM, Armonk, NY, USA) and the figures were drawn by GraphPad Prism 7 (GraphPad Software, San Diego, USA). Counted data were presented as (n, %) and analyzed by the chi-square test. Measured data were presented as ($\bar{x}$±s). The one-way ANOVA followed with LSD-post hoc test were performed for the comparison among multiple time points, and the independent samples t-test was adopted for the comparison between two groups. Paired-samples t-test was used for the comparison of two time points within groups. $P<0.05$ indicated a significant difference.

Table 1. Comparison of general information between groups

Group	Experimental group (n=60)	Control group (n=60)	χ^2/t	P
Age (years old)				
Range	36-70	35-69		
Mean age	50.11±2.65	50.23±2.50	0.255	0.799
Average weight (kg)	56.98±1.68	56.74±1.57	0.808	0.420
BMI (kg/m^2)	22.85±1.12	22.98±1.20	0.613	0.541
FIGO staging				
Stage II	22	24	0.141	0.707
Stage III	25	24	0.035	0.853
Stage IV	13	12	0.051	0.822
Pathologic types				
Endothelial-like carcinoma	8	9	0.069	0.793
Plasmacytoma	25	26	0.034	0.853
Mucinous carcinoma	15	14	0.046	0.831
Undifferentiated cancer	8	7	0.076	0.783
Transparent cell carcinoma	4	4	0.000	1.000
Place of residence			0.036	0.850
Urban	38	37		
Rural	22	23		
Monthly income (yuan)			0.034	0.854
≥ 4000	26	27		
<4000	34	33		
Marital Status			0.100	0.752
Married	54	55		
Unmarried/divorced/widowed	6	5		
Educational level			0.035	0.852
High school and below	36	37		
University and above	24	23		

Note: International Federation of Gynecology and Obstetrics (FIGO); Body mass index (BMI).

Results

Comparison of general information

The two groups presented no significant difference in general information (P>0.05), as shown in **Table 1**.

Comparison of short-term efficacy

The ORR and DCR of the experimental group were higher than those of the control group (P<0.05), as shown in **Table 2**.

Comparison of serum CA125, TNF-α, IL-6, and HE4 levels

There was no statistical difference in the serum CA125, TNF-α, IL-6, and HE4 levels between the experimental group and control group at T1 (all P>0.05). The experimental group had significantly lower levels of serum CA125, TNF-α, IL-6, and HE4 than the control group at T2 and T3 (all P<0.001), as shown in **Figure 1**.

Comparison of the incidence of adverse reactions

The number of patients with adverse reactions in the experimental group and the control group was 48 (80.0%) and 45 (75.0%), respectively. No statistical difference was observed in the incidence of adverse reactions between the two groups (P>0.05), as shown in **Table 3**.

Comparison of tumor metastasis

The number of cases with liver metastasis, lung metastasis, other metastasis, and no metastasis in the experimental group was 5 (8.3%), 4

Table 2. Comparison of short-term efficacy between groups [n (%)]

Group	CR	PR	SD	PD	ORR	DCR
Experimental group	42 (70.0)	8 (13.3)	5 (8.3)	5 (8.3)	50 (83.3)	55 (91.7)
Control group	30 (50.0)	5 (8.3)	12 (20.0)	13 (21.7)	35 (58.3)	47 (78.3)
χ^2	5.000	0.776	3.358	4.183	9.076	4.183
P	0.025	0.378	0.067	0.041	0.003	0.041

Note: objective remission rate (ORR); disease control rate (DCR); Complete response (CR); Partial response (PR); Stable disease (SD); Progressive disease (PD).

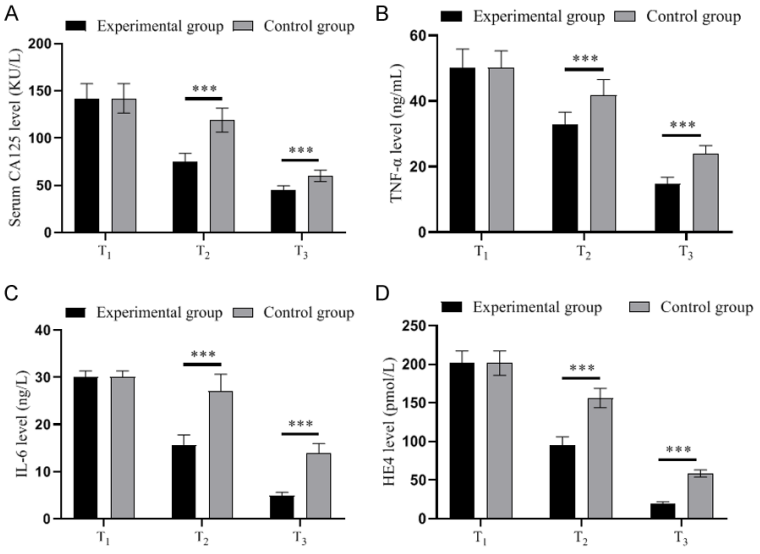

Figure 1. Comparison of serum CA125, TNF-α, IL-6, and HE4 levels. Note: A: Serum levels of CA125; B: Serum levels of TNF-α; C: Serum levels of IL-6; D: Serum levels of HE4. ***, P<0.001, between control group and experimental group by independent-samples t-test.

(6.7%), 1 (1.7%), and 50 (83.3%), respectively. The number of cases with liver metastasis, lung metastasis, other metastasis, and no metastasis in the control group was 8 (13.3%), 8 (13.3%), 4 (6.7%), and 40 (66.7%), respectively. The one-year follow-up revealed a significantly lower tumor metastasis rate in the experimental group compared to the control group (P< 0.05), as shown in **Table 4**. The CT images of patients are displayed in **Figure 2**.

Discussion

Ovarian cancer is a common malignancy with elusive pathogenesis. Currently, surgery and chemotherapy are the mainstays of treatment, and cytoreductive surgery combined with chemotherapy is required in most cases [16]. In this study, we used olaparib and paclitaxel in combination with carboplatin to treat ovarian cancer and achieved good results. Platinum drugs are the first choice of chemotherapy drugs for ovarian cancer, among which carboplatin, a second generation platinum compound, has a broad-spectrum antitumor effect, which can bind to the deoxyribonucleic acid of tumor cells to inhibit tumor cell proliferation and achieve killing effects [17]. However, due to the large size of the lesions after the fusion of the implanted metastases in advanced ovarian cancer, some patients may suffer adverse effects such as pelvic effusion after treatment, with no significant improvement in their long-term survival [18]. Thus, the combined use of carboplatin with other chemotherapeutic agents may potentiate the treatment efficiency. Sandercoek et al [19] reported paclitaxel combined with carboplatin regimen as a first-line regimen for stage III-IV ovarian epithelial cancer, whose overall efficiency can reach 90%. Relevant literature has shown that the efficiency of paclitaxel alone for ovarian cancer ranges 30.0%~40.0%, but it can exceed 60.0% in combination with platinum drugs [20]. The drug is a compound formed by the side chain and alkyl ring of paclitaxel, which can effectively increase the number of cytoplasmic microtubule dimers and accelerate the polymerization rate, thereby inhibiting the division and proliferation of tumor cells. In light of its potent synergistic effect with platinum drugs, paclitaxel is frequently used in combination with cisplatin in clinical practice. Moreover, carboplatin is non-neurotoxic compared with cisplatin, so the combination of paclitaxel and carboplatin has now become a first-line chemo-

Table 3. Comparison of the incidence of adverse reactions between groups [n (%)]

Group	Experimental group (n=60)	Control group (n=60)	χ^2	P
Total of adverse reactions	48 (80.0)	45 (75.0)	0.430	0.512
Leukopenia	48 (80.0)	45 (75.0)	0.430	0.512
Decreased hemoglobin	20 (33.3)	18 (30.0)	0.154	0.695
Impaired liver and kidney function	5 (8.3)	6 (10.0)	0.100	0.752
Nausea and vomiting	24 (40.0)	20 (33.3)	0.574	0.449
Thrombopenia	12 (20.0)	10 (16.7)	0.223	0.637
Hair loss	60 (100.0)	60 (100.0)	-	-
Peripheral neuritis	15 (25.0)	12 (20.0)	0.430	0.512
Anemia	14 (23.3)	12 (20.0)	0.196	0.658
Chest tightness	16 (26.7)	14 (23.3)	0.178	0.673
Other	10 (16.7)	8 (13.3)	0.261	0.609

Table 4. Comparison of tumor metastasis between groups [n (%)]

Group	Liver metastasis	Lung metastasis	Other metastasis	No metastasis
Experimental group	5 (8.3)	4 (6.7)	1 (1.7)	50 (83.3)
Control group	8 (13.3)	8 (13.3)	4 (6.7)	40 (66.7)
χ^2				3.654
P				0.001

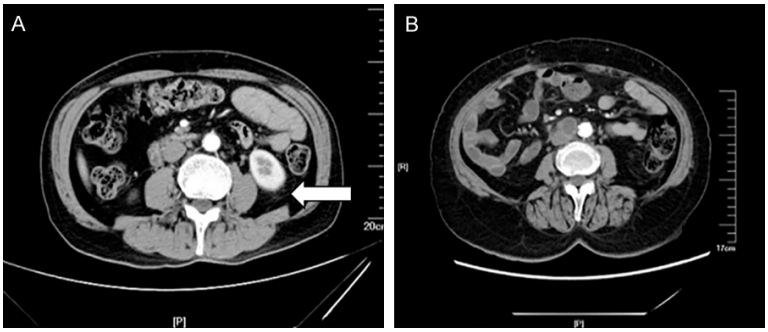

Figure 2. Typical CT images of patients. Note: A: Typical CT image of control group, where the white arrow indicates the abdominal neoplasm; B: Typical CT image of experimental group.

therapy regimen, with a higher safety profile [21].

In this study, the ORR and DCR of the experimental group were significantly higher than in the control group. Previous guidelines indicated that a PARP inhibitor, such asolaparib, can be used as an adjuvant drug for maintenance chemotherapy in ovarian cancer patients [22]. *In vitro* research has shown that olaparib can degrade tumors through a synthetic lethal program that prevents the accumulation of broken double strands of deoxyribonucleic acid in tumor cells and enhances genomic instability [23, 24].

In this study, the drug combination had good safety. In addition to tumor suppression, olaparib can also repair deoxyribonucleic acid damage after chemotherapy. However, no consensus has been developed in the domestic and international literature regarding the effects of olaparib on adverse effects in patients with ovarian cancer. It has been demonstrated that 97.95% of patients given olaparib experience adverse reactions (mostly grade I-II), with a higher incidence in China than in western countries, which is presumably related to the inability of domestic patients to adapt to the initial dose of olaparib recommended abroad due to their lower height, body mass, and surface area averages [25]. Accordingly, in this study, the dose of olaparib was set at 300 mg, 2 times/d. The results showed no statistical difference in the incidence of adverse reactions between the two groups, indicating that olaparib did not increase the inci-

dence of adverse reactions in patients, with a desirable safety profile as the drug was well tolerated. The limitation of this study is that the overall survival of patients and PFS failed to be accurately calculated due to the short inclusion time. In addition, it is a single institution study, which may have had researcher bias and subject selection bias. A multicenter and long follow-up study will be conducted in the future to obtain more clinical data.

Conclusion

Olaparib and paclitaxel combined with carboplatin can improve the serological indexes of patients with ovarian cancer, enhance disease control, and reduce the recurrence rate, with no extra toxic side effects.

Disclosure of conflict of interest

None.

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