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ORIGINAL ARTICLE

Comparisons of efficacy and safety between docetaxel + cisplatin and paclitaxel + cisplatin and their effects on serum HE4, CA125 and ROMA indicators in patients with ovarian carcinoma

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Summary

Purpose: *To explore the efficacy and safety of docetaxel (DTX) + cisplatin (DDP) and paclitaxel (TAX) + DDP and their effects on serum human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125) and risk of ovarian malignancy algorithm (ROMA) index in the treatment of ovarian carcinoma.*

Methods: *A total of 90 patients admitted and treated in our hospital from February 2017 to June 2018, with definitely diagnosed ovarian carcinoma via pathological biopsy were selected. The included patients were randomly divided into two groups: DTX+DDP group (n=45) and TAX+DDP group (n=45). With 3 weeks as a course, the treatments lasted for 6 consecutive courses. The changes in serum vascular endothelial growth factor (VEGF), matrix metalloproteinase 2 (MMP-2), HE4, CA125 and ROMA index were detected before and after treatments. Moreover, the incidence of adverse reactions was observed, and the clinical therapeutic efficacy was assessed.*

Results: *The clinical efficacy in both groups revealed that there were 39 and 34 cases obtained complete remission or partial remission in the DTX+DDP group and in the TAX+DDP group, respectively. Overall efficiencies were 86.67 and 75.56%, respectively, showing statistically significant differences between the two groups ($p<0.05$). The incidence rate of adverse reactions in DTX+DDP group was significantly lower than that in TAX+DDP group ($p<0.05$). The VEGF and MMP-2 levels in both DTX+DDP and TAX+DDP group were decreased compared with those before treatment (183.35±25.26 vs. 279.18±27.75 pg/mL and 228.22±40.21 vs. 316.11±33.6 pg/mL ($p<0.05$). The serum HE4 and CA125 levels and ROMA index in both groups were lower than those before treatment (121.19±14.14 vs. 159.43±18.15 pmol/L) ($p<0.05$), 239.45±25.37 vs. 288.37±30.36 pmol/L ($p<0.05$) and 58.02±6.61 vs. 76.23±11.58 ($p<0.05$), respectively). The above indicators were decreased in the DTX+DDP group to a significant extent ($p<0.05$).*

Conclusions: *Both DTX+DDP and TAX+DDP treatments are effective for the patients with ovarian carcinoma. However, DTX+DDP is more efficacious in lowering indicators such as serum CA125, HE4 and MMP-2 and ROMA index and adverse reactions, thus providing a more efficient practice scheme with lower toxic side effects for the clinical treatment of ovarian carcinoma.*

Key words: *docetaxel, paclitaxel, cisplatin, ovarian cancer, HE4, CA125*

Introduction

Ovarian carcinoma is one of the malignancies seriously threatening the life safety of women, and it is characterized by silent onset, relatively fast growth and early abdominal spread [1]. Carbohydrate antigen 125 (CA125) is currently the most common tumor marker that is used for early diag-

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nosis, treatment efficacy and prognosis assessment of ovarian carcinoma. Nevertheless, serum CA125 is also elevated in patients with some benign ovarian tumors, so it lacks cancer specificity. Human epididymis protein 4 (HE4) is an acidic small-molecular protein found in human epididymal epithelial cells, and it is barely expressed in normal ovarian tissues and non-ovarian tumors, while it is highly expressed in the serum of patients with ovarian carcinoma, thus serving as a specific marker of ovarian carcinoma [2]. Studies have revealed that tumor angiogenesis helps diffusion and metastasis of ovarian carcinoma and that vascular endothelial growth factor (VEGF) and matrix metalloproteinase 2 (MMP-2) play important roles in promoting tumor angiogenesis [3,4], and their serum levels in patients with ovarian carcinoma are obviously elevated [5,6]. Surgery is the preferred treatment method for ovarian carcinoma, however postoperative recurrence is quite frequent, so that chemotherapy regimens, such as docetaxel (DTX) + cisplatin (DDP) and paclitaxel (TAX) + DDP are usually utilized to decrease the recurrence rates [7].

This study compared and analyzed the efficacy and safety of both DDP+DTX and DDP+TAX and their influence on serum VEGF, MMP-2, HE4 and CA125 and risk of ovarian malignancy algorithm (ROMA) index in treating patients with ovarian carcinoma, hoping to provide a reference for selecting more effective and safe treatment regimens in clinical practice.

Methods

Study subjects and grouping

A total of 90 patients admitted and treated in our hospital from February 2017 to June 2018, who were definitely diagnosed with ovarian carcinoma via imaging and pathological examination were selected. The included patients were randomly divided into two groups: DTX+DDP group (n=45) and TAX+DDP group (n=45). All of the patients signed informed consent, and the study was approved by the Ethics Committee of Xuzhou Medical University Affiliated Hospital of Lianyungang.

Inclusion and exclusion criteria

Inclusion criteria: 1) ovarian cancer confirmed by imaging examination and pathological studies; 2) TNM stage for IV; 3) More than 18 years old; 4) Complete patient data and complete auxiliary examinations. Exclusion criteria: 1) Primary organ dysfunction; 2) Secondary ovarian cancer; 3) Loss of follow-up; 4) Pregnant or lactating women; 5) Failure to complete the chemotherapy regimen due to serious complications.

Study methods

The patients in DTX+DDP group were administered intravenously DTX (70 mg/m^2) for 1 h on the first day of treatment and DDP infusion (30 mg/m^2) for 6 h on the second day every 3 weeks. Those in the TAX+DDP group were administered intravenously TAX (135 mg/m^2) for 24 h on the first day of treatment and DDP infusion (30 mg/m^2) for 6 h on the second day every 3 weeks. The patients were scheduled to receive 6 consecutive cycles. Both groups of patients were subjected to routine blood, liver and kidney function tests and electrocardiogram before and after each chemotherapy cycle, so as to evaluate the toxic reactions and conduct symptomatic treatments timely.

Measurement of serum VEGF, MMP-2, HE4 and CA125 levels

The levels of serum VEGF, MMP-2, HE4 and CA125 in the two groups of patients were determined before and after treatments using the Tecan Infinite M1000 Pro Microplate Reader (TECAN, Männedorf, Switzerland). The corresponding ROMA index was automatically calculated by the ROMA analysis software.

Assessment of clinical efficacy

Assessment of clinical efficacy was based on the Response Evaluation Criteria in Solid Tumors (RECIST) [8], as follows:

1. Complete remission: Lesion disappears with normal tumor markers, lasting for at least 4 weeks.
2. Partial remission: The maximum lesion diameter is decreased by no less than 30%, with tumor markers higher than normal levels, lasting for at least 4 weeks.
3. Stable disease: The maximum lesion diameter is decreased by less than 30% or increased by no more than 20%, lasting for at least 4 weeks.
4. Progressive disease: The maximum lesion diameter is increased by more than 20% or new lesions are discovered.

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used to process the data results. The measurement and count data were expressed as mean ± standard deviation and ratio (%), respectively. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of general clinical characteristics

General characteristics such as age, family history, grade of tumor differentiation, metastatic spread and clinical stage were compared between the two groups of patients, and the results showed that the differences were not statistically significant ($p>0.05$) and comparable (Table 1).

Comparisons of VEGF and MMP-2 levels before and after treatments between the two groups

The VEGF and MMP-2 levels were compared before and after treatment. Their levels decreased

in both groups (183.35±25.26 *vs.* 279.18±27.75 pg/mL and 228.22±40.21 *vs.* 316.11±33.66 pg/mL), and this decrease was more pronounced in the DTX+DDP group (p<0.05). These results showed that DTX+DDP could inhibit tumor metastasis more efficiently, thus improving the prognosis of patients with ovarian carcinoma (Figures 1,2).

Comparison of clinical efficacy

The clinical efficacy in the two groups is shown in Table 2. In the DTX+DDP group there were 39 cases achieving complete or partial remission. Overall efficacy in the DTX+DDP group and TAX+DDP group was 86.67% and 75.56%, respectively (p<0.05), suggesting that the DTX+DDP regimen has a stronger antitumor effect (Table 2).

Comparisons of adverse reactions between the two groups

The incidence rates of gastrointestinal reactions, severe myelosuppression and neurotoxicity in the DTX+DDP group and the TAX+DDP group were 82.22 *vs.* 91.11%, 53.33 *vs.* 73.33% and 28.89 *vs.* 55.56%, respectively. The toxic side effects in the DTX+DDP group were significantly milder (p<0.05) (Table 3).

Table 1. Comparison of general clinical information between the two groups

Group	*n*	*Age (years)*	*Family history (n)*	*Differentiation degree (n)*			*Metastasis site (n)*		
				Low	*Middle*	*High*	*Pelvic*	*Liver, kidney and lung*	*Other sites*
DTX+DDP group	45	48.13±8.45	2	7	20	18	40	5	3
TAX+DDP group	45	49.19±9.18	1	6	19	20	43	7	2

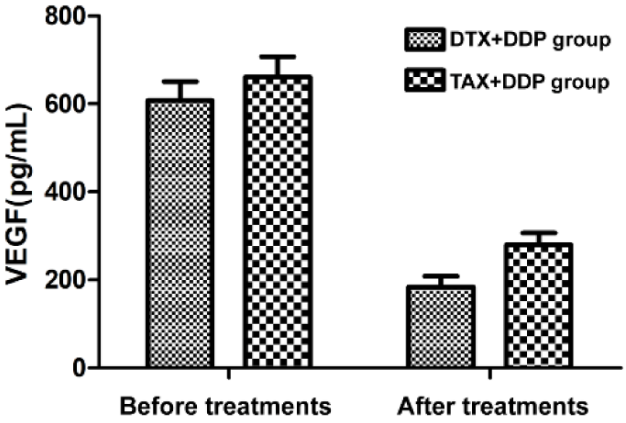

Figure 1. Comparison of VEGF level before and after treatment between the two groups (p<0.05).

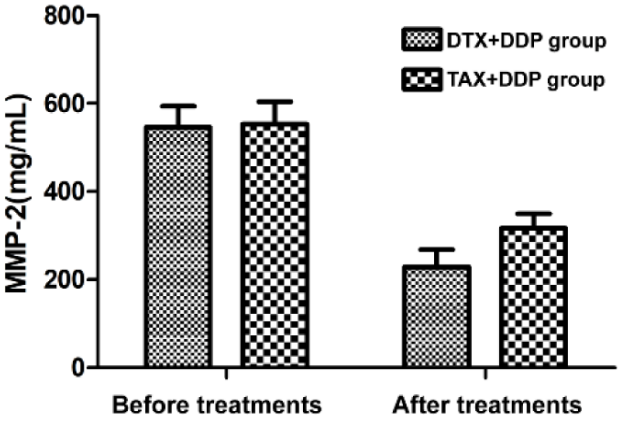

Figure 2. Comparison of MMP-2 level before and after treatment between the two groups (p<0.05).

Table 2. Comparison of responses between the two groups

Group	*n*	*Complete remission n (%)*	*Partial remission n (%)*	*Stable disease n (%)*	*Progressive disease n (%)*
DTX+DDP	45	10 (22.22)	29 (64.44)	5 (11.1)	1 (2.22)
TAX+DDP	45	8 (17.77)	26 (57.77)	8 (17.77)	3 (6.67)

Table 3. Comparison of adverse reactions between the two groups

Group	*n*	*Gastrointestinal reactions n (%)*	*Alopecia n (%)*	*Severe myelosuppression n (%)*	*Neurotoxicity n (%)*	*Liver and kidney damage n (%)*
DTX+DDP	45	37 (82.22)	11 (24.44)	24 (53.33)	13 (28.89)	9 (20.00)
TAX+DDP	45	41 (91.11)	14 (31.11)	33 (73.33)	24 (55.56)	12 (26.67)
x^2		4.126	0.989	5.978	7.669	1.312
p		<0.05	>0.05	<0.05	<0.05	>0.05

Table 4. Comparison of serum HE4 and CA125 levels and ROMA index before and after treatments between the two groups

Group		*HE4 (pmol/L)*	*CA125 (pmol/L)*	*ROMA index (%)*
DTX+DDP	Before treatment	200.03±20.19	328.52±35.45	88.16±13.15
	After treatment	121.19±14.14 [a,b]	239.45±25.37 [a,b]	58.02±6.61
TAX+DDP	Before treatment	202.02±24.81	331.11±41.32	90.84±12.28
	After treatment	159.43±18.15 [a]	288.37±30.36 [a]	76.23±11.58

[a]p<0.05 *vs.* before treatments; [b]p<0.05 between the two groups

Comparisons of serum HE4 and CA125 levels and ROMA index before and after treatment between the two groups

After treatment, the serum HE4 and CA125 levels and ROMA index in the DTX+DDP and TAX+DDP groups were lower than those before treatment (121.19±14.14 *vs.* 159.43±18.15 pmol/L, 239.45±25.37 *vs.* 288.37±30.36 pmol/L, and 58.02±6.61 *vs.* 76.23±11.58), suggesting that the decrease in the DTX+DDP group was more pronounced (p<0.05) (Table 4).

Discussion

Ovarian carcinoma has a high recurrence rate and low survival, so selecting appropriate postoperative chemotherapy regimens is vital for inhibiting the recurrence and reducing toxic reactions. Taxanes, as the main chemotherapy drugs for the current clinical treatment of ovarian cancer, stably bind to tubulins and suppress their depolymerization, thus exerting an antitumor effect [9]. Compared with TAX, DTX, a newer-generation taxane, has a stronger capacity to bind to tubulins, and *in vitro* experiments have shown that it accumulates in cells at high concentration and that its killing effect on tumor cells is 3 times stronger than that of TAX [12]. Additionally, DTX creates less allergic reactions and neurotoxicity, and especially less leukopenia [13]. DDP, as a cell cycle nonspecific agent, can damage DNA, trigger apoptosis of tumor cells and repress their reproduction process *in vivo* [14]. Combining taxanes with DDP can increase the disease-free survival rate of patients without cross-resistance [15].

VEGF and MMP-2 are key factors which contribute to tumor angiogenesis, invasion and metastasis, and substantially raised VEGF and MMP-2 levels are detected in the serum of the patients with malignant ovarian carcinoma, which are positively proportional to the severity of the disease [16,17]. After standard chemotherapies, both VEGF and MMP-2 were lowered in the DTX+DDP group and TAX+DDP group [(183.35±25.26 *vs.* 279.18±27.75) pg/mL and (228.22±40.21 *vs.* 316.11±33.66) pg/mL] compared with those before treatments. Moreover, the degree of decrease was more obvious in the DTX+DDP group, showing statistically significant differences between the two groups (p<0.05). It is inferred that DTX+DDP may inhibit tumor tissue metastasis better, thus helping improve prognosis.

In this study, the overall efficiency in DTX+DDP group and in TAX+DDP group were 86.67% and 75.56%, respectively. The inter-group differences were statistically significant (p<0.05), suggesting that DTX+DDP is more effective treatment for ovarian carcinoma. Patients in both groups were subjected to routine blood tests, liver and kidney function tests and electrocardiogram examinations before and after each chemotherapy cycle, so as to understand the toxic reactions and conduct symptomatic treatments timely. There were no patients whose chemotherapies were suspended due to adverse reactions in both groups. The incidence rates of gastrointestinal reactions, severe myelosuppression and neurotoxicity in the DTX+DDP group and TAX+DDP group were 82.22 *vs.* 91.11%, 53.33 *vs.* 73.33% and 28.89 *vs.* 55.56%, respectively. It can be seen that the toxic side effects in the DTX+DDP group were significantly milder (p<0.05), so DTX+DDP is more conducive to improving the patient quality of life.

Testing serum tumor markers can help find patients with atypical symptoms and small tumors at an early stage. Their expression levels in serum are directly associated with the occurrence, development and prognosis of ovarian carcinoma. Among them, CA125 has high sensitivity and is notably decreased after radical tumor resection, but its expression level in some ovarian tumors is not raised due to low specificity [18]. Besides, the expression level of HE4 in ovarian carcinoma is obviously higher than that in non-ovarian tumors. Recent studies have demonstrated that the combined detection of CA125 and HE4 is of

great value for the early diagnosis and prognosis assessment, and ROMA index can be further calculated to help determine the high risk of ovarian carcinoma [19,20]. According to the experimental results in this study, the serum HE4 and CA125 levels and ROMA index in the DTX+DDP and TAX+DDP groups were lower than those before treatments [(121.19±14.14 *vs.* 159.43±18.15 pmol/L), (239.45±25.37 *vs.* 288.37±30.36 pmol/L, (58.02±6.61 *vs.* 76.23±11.58%], with more obvious degrees of decreases in the DTX+DDP group ($p<0.05$), further revealing that the killing effect of DTX+DDP on tumor cells is stronger.

Conclusions

In conclusion, the treatments with DTX+DDP and TAX+DDP are both effective for the patients with ovarian carcinoma. However, DTX+DDP is more effective in lowering serum CA125, HE4, MMP-2 and ROMA index and adverse reactions, thus providing a more efficient practice scheme with lower toxic side effects for the clinical treatment of ovarian carcinoma.

Conflict of interests

The authors declare no conflict of interests.

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