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Efficacy of cisplatin plus paclitaxel as chemotherapy in patients with cervical cancer after laparoscopic nerve-sparing extensive hysterectomy and its effect on immune function

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Abstract: To investigate the value of cisplatin plus paclitaxel in patients with middle and advanced cervical cancer after laparoscopic nerve-sparing extensive hysterectomy and its effect on their T lymphocyte subsets. 44 patients with middle and advanced cervical cancer were randomly divided into the control group (n = 22) and the observation group (n = 22). Patients in the control group received nab-paclitaxel as chemotherapy, while patients in the observation group received cisplatin plus nab-paclitaxel as adjuvant therapy. The local recurrence and distant metastasis rates were statistically analyzed after 1 year of follow-up. The overall effective rate in the observation group was significantly higher than that in the control group ($P<0.05$). The serum levels of IL-4, IL-10 and TNF-α in the two groups were reduced markedly after treatment than before treatment ($P<0.05$) and the observation group was significantly lower than the control group ($P<0.05$). After treatment, the proportion of $CD3^+$ and $CD4^+$ cells increased, the proportion of $CD8^+$ cells decreased more significantly than that in the control group ($P<0.05$). The combination of cisplatin and paclitaxel was demonstrated to have obviously synergistic and attenuated effects after middle and advanced cervical cancer surgery, optimize the efficacy, reduce adverse effects, and improve the body's immune function.

Keywords: Cervical cancer, middle and advanced stage, paclitaxel, cisplatin, T lymphocyte subsets.

INTRODUCTION

Cervical cancer is currently one of the major diseases endangering human health (Rosen *et al*., 2017). With the constant advancement of surgical procedures, the survival rate of cervical cancer has witnessed a uptrend (Tewari *et al*., 2017). At present, there are diverse therapies for cervical cancer. Most patients obtain a favorable outcome with surgery in the early stages of cancer, and still some patients require chemoradiotherapy as adjuvant therapy on the basis of surgery (Heeren *et al*., 2019). Cisplatin, a second-generation platinum-based chemotherapeutic agent, exhibits a broad anti-tumor spectrum and a high safety profile in its basic study, yet its utlity in the treatment of cervical cancer is marginally studied due to its restricted indications (Li *et al*., 2019). Paclitaxel has been demonstrated to be a good radiosensitizer. Paclitaxel/cisplatin combination chemotherapy was demonstrated to have superior progression-free survival than platinum alone in some phase III studies. However, the combination has yet been marginally explored in middle and advanced cervical cancer after laparoscopic nerve-sparing extensive hysterectomy. To this end, this study was designed to investigate the value of cisplatin plus paclitaxel as chemotherapy in patients with middle and advanced cervical cancer after laparoscopic nerve-sparing extensive hysterectomy and its effect on their T lymphocyte subsets.

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MATERIALS AND METHODS

General data

44 patients with middle and advanced cervical cancer after laparoscopic nerve-sparing extensive hysterectomy from June 2018 to June 2019 were selected as study subjects. Patients were numbered according to the order of admission and randomly divided into the control group and the observation group, with 22 cases in each group. Control group: aged 26 - 69 years, (45.2±6.3) years on average; body weight (64.2±9.8) kg; 19 cases of squamous cell carcinoma and 3 cases of adenocarcinoma in histological types; 13 cases of cervical cancer stage II and 9 cases of stage III. Observation group: aged 25 - 68 years, (46.3±7.4) years on average; body weight (65.3±9.7) kg; 18 cases of squamous cell carcinoma and 4 cases of adenocarcinoma in histological types; 12 cases of cervical cancer stage II and 11 cases of stage III. No statistically significant difference was observed in the clinical data between the two groups ($P>0.05$).

Inclusion criteria (Tao *et al*., 2020): Patients who met the diagnostic criteria of cervical cancer in the Guidelines for Standardized Diagnosis and Treatment of Cervical Cancer and Precancerous Lesions (Trial), and confirmed by pathological tissue or cytology; Patients who aged > 18 years, and with expected survival of more than 6 months; Patients with clinical stage II-III by referring to the International Clinical Stage of Cervical Cancer adopted by the International Federation of Obstetrics and

Gynecology; Patients who did not receive chemo radiotherapy intervention before enrollment; Patients were well-informed and voluntarily signed the consent form. This study was approved by the Ethics Committee of our hospital.

Exclusion criteria: Patients with severe circulatory system diseases; Patients with severe heart, liver, kidney, lung and hematopoietic system diseases; Patients with mental illness; Patients who has taken anti-cancer traditional Chinese medicine preparations, biological agents and immunomodulatory drugs 4 weeks before enrollment; Patients with other malignant tumors; Patients who were pregnant or lactating women; Patients who were allergic to this medication; Patients who were unable to cooperate with the treatment and follow-up.

Specific operation of laparoscopic nerve-sparing extensive hysterectomy (Nakamura *et al*., 2019): After general anesthesia, a 1.5-cm incision was made at the site of the upper edge of the umbilical chakra, a 10-mm puncture cannula was inserted and a CO2 pneumoperitoneum was established with a pressure of 12 - 13 mmHg. Then, 3-4 operating puncture cannulas were placed on both sides of the lower abdomen, the pelvic lymph nodes on both sides were removed in whole blocks under laparoscopy, the iliac vessels and ureter were fully exposed, the lateral rectal space was separated by ultrasonic knife, the Ganglin space between the ureteral tract and the uterosacral ligament was separated to reveal the infra-abdominal nerve below it. After the utero-rectal peritoneum was transected by ultrasonic knife, the vaginal-rectal space was separated bluntly and sharply, incision of peritoneum between rectum and sacral ligament was performed, the sacral ligament was cut for 3 cm preserving the inferior abdominal nerve below and laterally. The bladder was opened and the peritoneal reflex was pushed down to 4 cm below the vaginal vault; the lateral bladder space was opened, the uterine artery was freed, and the uterine artery and superficial uterine vein were cut after electro coagulation at the beginning of the uterine artery.

Then the nutritive branch of the ureter was cut along the underside of the uterine artery with the ultrasonic knife, the ureter was freed and the anterior lobe of the cervical ligament of the bladder was cut in stages. The paravaginal space was opened, the deep uterine vein was freed from the internal iliac vein medially, clip or bipolar electro coagulated at 1 cm from the internal iliac vein, the deep uterine vein was cut, followed by the main ligament medially immediately below the deep uterine vein, freed and the middle bladder vein and the inferior bladder vein were bipolar electro coagulated and other branches in the posterior lobe of the cervical ligament of the bladder, continued to fully push down the bladder. The paravaginal vein was cut after bipolar electro coagulation and the pelvic autonomic nerve uterine branch was severed so that the bladder autonomic nerve fibers were fully preserved; the vaginal vault was ligated and the vagina was severed for 3 cm. After removal of the specimen from the vagina, the vaginal stump was closed with absorbable sutures, the pelvic cavity was thoroughly irrigated and a drainage tube was placed, and antibiotics were administered according to specifications.

Chemotherapy method

1. Observation group. Patients were routinely administered dexamethasone, cimetidine, etc. orally Afterwards, patients were administered 135 mg/m2 paclitaxel (manufactured by Bristol-Myers Squibb (China) Investment Co., Ltd.) by intravenous drip for at least 3 hours on Day 1, and 25 mg/m2 cisplatin (manufactured by Yunnan Gejiu Biological Pharmaceutical Co., Ltd.) by intravenous drip on Days 1-3 for every 4 weeks cycle.

2. Control group. Patients were administered 25 mg/m2 cisplatin by intravenous drip on Days 1 - 3, and 500 mg/m2 fluorouracil by intravenous drip on Days 1 - 5 for every 4 weeks cycle. Patients were also given conventional treatment, including fluid replacement and antiemetic therapy.

Response evaluation criteria

Efficacy the treatment effect was assessed 1 week after the end of treatment in both groups, with reference to the *Response Evaluation Criteria in Solid Tumors*. Complete response (CR): complete disappearance of measurable lesions, lasting for ≥ 4 weeks; partial response (PR): measurable lesions shrink by more than 1/2 after treatment, lasting for > 4 weeks without new lesions; stable disease (SD): ≤ 1/2 reduction and ≤ 1/4 increase in the size of measurable lesions, without new lesions; progressive disease (PD): >25% increase in the size of measurable lesions, or the presence of new lesions. Overall response rate = (CR + PR)/total number of cases × 100%.

Adverse effects: The occurrence of adverse effects in the two groups was statistically analyzed according to the grading criteria for chemotherapy-induced adverse effects defined by World Health Organization.

T lymphocyte subsets. Three milliliters of peripheral venous blood was collected before treatment and 1 week after the end of treatment; CD3+, CD4+ and CD8+ were determined by Cyto FLEX flow cytometry (Beckman Coulter, USA), and CD4+/CD8+ ratio was calculated. Changes in inflammatory mediators before and after treatment were observed in the two groups. Four milliliters of peripheral venous blood was drawn before and after treatment, separated and centrifuged at 2500 r/min.

Table 1: Comparison of the recent efficacy between the two groups [n (%)]

Groups	N	PD	SD	PR	CR	Overall
Observation group	22	1	5	9	7	16
Control group	22	5	7	6	4	10
$\chi 2$						4.674
P						0.03

Table 2: Comparison of T lymphocyte subsets between the two groups

Groups	N	CD3+		CD4+		CD8+	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	22	43.86±5.31	61.25±4.34	44.27±4.82	55.12±4.92	40.62±4.75	31.25±4.17
Control group	22	45.45±3.28	52.51±4.76	42.38±4.67	47.17±4.31	41.76±3.85	36.52±4.28
t		-1.027	4.547	1.621	6.326	-0.511	3.841
P		0.325	≤0.01	0.053	≤0.01	0.563	≤0.01

Table 3: Comparison of cytokine changes between the two groups

Groups	N	IL-4		IL-10		TNF-α	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	22	29.82±4. 27	9.32±2.09	22.46±4.13	10.47±1.85	18.42±2.95	8.07±0.42
Control group	22	29.39±5.83	16.43±3.11	22.61±4.07	17.19±1.97	18.39±2.14	11.83±0.51
t		0.503	-15.186	0.396	-16.217	0.247	12.859
P		0.246	≤0.01	0.307	≤0.01	0.475	≤0.01

Table 4: Comparison of adverse effects between the two groups

Groups	N	Anemia	Gastrointestinal reactions	Leukopenia	Alopecia	Impaired renal function
Observation group	22	3	2	2	4	5
Control group	22	6	5	10	7	9
$\chi 2$		2.651	1.872	0.874	3.872	3.986
P		0.301	0.498	0.707	0.219	0.197

The levels of interleukin (IL) -4, IL-10 and tumor necrosis factor (TNF) -α were measured by enzyme-linked immunosorbent assay (ELISA). Patients in both groups received a 1-year follow-up, with a deadline of June 15, 2020 and their recurrence rate and distant metastasis rate during the follow-up period were recorded.

STATISTICAL ANALYSIS

SPSS23.0 software was used for data processing. Measurement data were presented as mean ± standard deviation, and t-test was used for the comparison between groups. Enumeration data were presented as (%) and $\chi 2$ test was used for the comparison between groups. $P<0.05$ indicated a statistically significant difference.

RESULTS

Clinical efficacy the observation group yielded a better response rate than the control group and the difference was statistically significant ($\chi 2 = 4.674$, $P<0.05$) (table 1).

T lymphocyte subsets

After treatment, the proportion of CD3+ and CD4+ cells increased, the proportion of CD8+ cells decreased, and the CD4+/CD8+ ratio increased in the observation group ($P<0.05$). The proportion of CD3+ and CD4+ cells and the CD4+/CD8+ ratio in the observation group were higher than those in the control group and the proportion of CD8+ cells was lower than that in the control group, and the comparison between groups was statistically significant ($P<0.05$) (table 2).

Comparison of cytokine changes between the two groups

There were no notable differences in serum levels of IL-4, IL-10 and TNF-α before treatment between the two groups ($P>0.05$). The serum levels of IL-4, IL-10 and TNF-α in the two groups were reduced markedly after treatment than before treatment ($P<0.05$) and the observation group was significantly lower than the control group ($P<0.05$) (table 3).

Adverse effects

The incidences of anemia, gastrointestinal reactions, leukopenia and alopecia in the observation group were lower than those in the control group, but the difference was insignificant ($P>0.05$) (table 4).

Recurrence and metastasis rate during follow-up

During follow-up, the observation group had 1 case (4.5%) of recurrence and 2 cases (9.1%) of metastasis, while the control group had 2 cases (9.1%) of recurrence and 5 cases (22.7%) of metastasis. The recurrence and metastasis rate in the observation group were slightly lower than that in the control group, but the difference had no statistical significance (P>0.05).

DISCUSSION

Cervical cancer is one of the gynecologic malignancies with high clinical incidence. According to relevant data, there are about 500,000 new cases of cervical cancer worldwide each year, and there is a rising trend of its occurrence in youth. More and more women's health is threatened by cervical cancer in recent years (Marquina *et al*., 2018; Yu *et al*., 2020). At present, there are many clinical therapies for cervical cancer (Mao *et al*., 2019; Yavas *et al*., 2019). The basic therapy for cervical cancer is platinum-based in combination with chemotherapy (Buyukkoroglu *et al*., 2019). The pharmacological action of cisplatin as a second-generation platinum-based drug can exert alkylation on tumor cells, aggregating and shrinking them until their lysis and apoptosis occur. Its cytotoxic effect works well in human tumor cell lines. Meanwhile, loplatin is effective in identifying and protecting normal cells in humans (Zhang *et al*., 2020). Neoadjuvant chemotherapy with paclitaxel + cisplatin is found to increase the long-term survival of patients with advanced cervical cancer after surgery (Liu *et al*., 2019). In terms of chemotherapeutic drugs, paclitaxel and cisplatin are effective drugs for the treatment of advanced cervical cancer. Paclitaxel is a novel anti-microtubule drug that maintains tubulin stability, inhibits cell mitosis, blocks tumor cell division and reproduction, and inhibits depolymerization by the promotion of tubulin polymerization (Wang *et al*., 2019). The results of this study showed that the overall efficacy rate in the observation group was significantly higher than that in the control group (P<0.05). There were much fewer cases presenting observed adverse effects in the observation group as compared to the control group.

IL-4 functions as a regulator of the human immune system, primarily through adaptive and regulatory immunity. It is secreted mainly by Th2 cells, achieving relief mainly through immunomodulation (Seber *et al*., 2020). However, over expression of IL-4 will cause an overproduction of IL-10 in the tumor, thereby leading to a disruption of the immune system and an inability to control tumor growth. IL-10 may reduce the activity of natural killer (NK) cells mainly through the inhibition of interferon-γ, and inhibit the growth and reproduction of anti-tumor factors to allow tumors to develop, metastasize and spread *in vivo* (Li *et al*., 2018). TNF-α is mainly secreted by macrophages after stimulation, which can effectively destroy tumor cells and thus exert anti-tumor effects. Studies have reported that TNF-α expression is higher in patients with malignant tumors than in normal subjects (Wei *et al*., 2017). This study showed (Zagouri *et al*., 2019) that cisplatin combined with paclitaxel regimen can alleviate the inflammatory response by decreasing the levels of IL-4, IL-10 and TNF-α. T-cell, consisting of two main subsets (CD4+ and CD8+), being prerequisite for maintaining normal immune function in the body. Studies have reported that cellular immune function is significantly lower in patients with cervical cancer, suggesting the presence of cellular immune dysfunction in patients with cervical cancer (Kumar *et al*., 2018; Qiu *et al*., 2018). This study highlighted that changes in CD3+, CD4+ and CD4+/CD8+ after treatment were higher in the observation group than in the control group, which indicated that the immune function of the patients was greatly enhanced by chemotherapy with cisplatin combined with paclitaxel.

CONCLUSION

In summary, the combination of cisplatin and paclitaxel is a preferable option for patients after middle and advanced cervical cancer surgery and serves to optimize the efficacy, reduce adverse effects and enhance immune function.

REFERENCES

Buyukkoroglu G, Şenel B and Yenilmez E (2019). Vaginal suppositories with siRNA and paclitaxel-incorporated solid lipid nanoparticles for cervical cancer: Preparation and *in vitro* evaluation. *Methods Mol Biol*. **1974**: 303-328.

Heeren AM, van Luijk IF and Lakeman J (2019). Neoadjuvant cisplatin and paclitaxel modulate tumor-infiltrating T cells in patients with cervical cancer. *Cancer Immunol Immunother*., **68**(11): 1759-1767.

Kumar L, Harish P, Malik PS and Khurana S (2018). Chemotherapy and targeted therapy in the management of cervical cancer. *Curr. Probl. Cancer*, **42**(2): 120-128.

Li J, Chen L, Liu Q, Tang M, Wang Y and Yu J (2018). Buformin suppresses proliferation and invasion via AMPK/S6 pathway in cervical cancer and synergizes with paclitaxel. *Cancer Biol. Ther*., **19**(6): 507-517.

Li J, Chen Q and Deng Z (2019). KRT17 confers paclitaxel-induced resistance and migration to cervical cancer cells. *Life Sci*., **224**: 255-262.

Liu JJ, Ho JY and Lee HW (2019). Inhibition of phosphatidylinositol 3-kinase (pi3k) signaling synergistically potentiates antitumor efficacy of paclitaxel and overcomes paclitaxel-mediated resistance in cervical cancer. *Int. J. Mol. Sci*., **20**(14): 3383.

Mao BD, Xu P, Xu P, Zhong Y, Ding WW and Meng QZ (2019). LINC00511 knockdown prevents cervical

cancer cell proliferation and reduces resistance to paclitaxel. *J. Biosci*., **44**(2): 44.

Marquina G, Manzano A and Casado A (2018). Targeted agents in cervical cancer: beyond bevacizumab. *Curr. Oncol. Rep*., **20**(5): 40.

Nakamura F, Seino M and Suzuki Y (2019). Successful management of cutaneous lymphangitis carcinomatosa arising from cervical cancer with paclitaxel-cisplatin and bevacizumab combination therapy: A case report and review of the literature. *J. Med. Case Rep*., **13**(1): 328.

Qiu H, Li J, Liu Q, Tang M and Wang Y (2018). Apatinib, a novel tyrosine kinase inhibitor, suppresses tumor growth in cervical cancer and synergizes with Paclitaxel. *Cell Cycle*. **17**(10): 1235-1244.

Rosen VM, Guerra I and McCormack M (2017). Systematic review and network meta-analysis of bevacizumab plus first-line topotecan-paclitaxel or cisplatin-paclitaxel versus non-bevacizumab-containing therapies in persistent, recurrent, or metastatic cervical cancer. *Int. J. Gynecol Cancer*. **27**(6): 1237-1246.

Seber S, Sirin DY, Yetisyigit T and Bilgen T (2020). Piperlongumine increases the apoptotic effect of doxorubicin and paclitaxel in a cervical cancer cell line. *Niger J. Clin. Pract*., **23**(3): 386-391.

Tao W, Yang J, Jiang Y, Chen W and Wang Y (2020). Paclitaxel, carboplatin and bevacizumab in advanced cervical cancer: a treatment response and safety analysis. *Dose Response*. **18**(3): 1559325820941351.

Tewari KS, Sill MW and Penson RT (2017). Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. **390**(10103): 1654-1663.

Wang YT, Li B, Li XG, Ma SK, Zhang R and Wu LY (2019). fficacy and side effect analysis of paclitaxel liposome for neoadjuvant chemotherapy in locally advanced cervical cancer. *Zhonghua Fu Chan Ke Za Zhi*., **54**(9): 588-594.

Wei Y, Pu X and Zhao L (2017). Preclinical studies for the combination of paclitaxel and curcumin in cancer therapy (Review). *Oncol. Rep*., **37**(6): 3159-3166.

Yavas G, Yavas C, Sen E, Oner I, Celik C and Ata O (2019). Adjuvant carboplatin and paclitaxel after concurrent cisplatin and radiotherapy in patients with locally advanced cervical cancer. *Int. J. Gynecol Cancer*. **29**(1): 42-47.

Yu J, Zhao Y and Liu C (2020). Synergistic anti-tumor effect of paclitaxel and miR-34a combined with ultrasound microbubbles on cervical cancer *in vivo* and *in vitro*. *Clin. Transl. Oncol*., **22**(1): 60-69.

Zagouri F, Korakiti AM and Zakopoulou R (2019). Taxanes during pregnancy in cervical cancer: A systematic review and pooled analysis. *Cancer Treat Rev*., **79**: 101885.

Zhang L, Zheng CY, Cao JH and Luo SL (2020). Efficacy of paclitaxel, carboplatin and bevacizumab for cervical cancer: A protocol for systematic review and meta-analysis. *Medicine* (Baltimore), **99**(24): e20558.