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ORIGINAL ARTICLE

Influences of neoadjuvant chemotherapy on clinical indicators, prognosis and neutrophil/lymphocyte ratio of stage IB2-IIB cervical cancer

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Summary

Purpose: *To investigate the influence of neoadjuvant chemotherapy on the efficacy, clinical indicators, prognosis and neutrophil/lymphocyte ratio (NLR) of stage IB2-IIB cervical cancer.*

Methods: *120 cervical cancer patients were selected and randomly divided into the control group (n=60) and the observation group (n=60). The patients in the observation group were treated with neoadjuvant chemotherapy combined with surgery, while those in the control group received treatment with surgery alone. The serum tumor markers [matrix metalloproteinase-9 (MMP-9), carcino-embryonic antigen (CEA) and cancer antigen 125 (CA-125)], immunoglobulins (Igs) (IgA and IgM), T-lymphocyte subsets [cluster of differentiation (CD) 4$^+$, CD8$^+$ and CD4$^+$/CD8$^+$], NLR, quality of life, change in cancer-related fatigue degree and clinical efficacy were compared before and after treatment between the two groups.*

Results: *The levels of MMP-9, CEA, CA-125, NLR, IgA, IgM, CD4$^+$ CD8$^+$, CD4$^+$/CD8$^+$ and Cancer Fatigue Scale (CFS) were decreased, while the World Health Organization Quality of Life Scale Brief (WHOQOL-BREF) score was increased in both groups after treatment, and the observation group exhibited more apparent changes in those levels than the control group ($p<0.05$). The effective rate was higher, but the incidence rates of postoperative lymphatic metastasis, vascular invasion, parametrial invasion and positive margin were lower in the observation group than those in the control group ($p<0.05$). The observation group had longer survival time than the control group ($p<0.05$).*

Conclusion: *Neoadjuvant chemotherapy can effectively lower the levels of serum tumor markers and NLR, reduce the metastasis rate of cancer cells and the degree of cancer-related fatigue after operation, improve the quality of life and prolong the survival time.*

Key words: *neoadjuvant chemotherapy, cervical cancer, tumor markers, immune function, NLR, prognosis and efficacy*

Introduction

Cervical cancer is the second major gynecological malignant tumor, right next to breast cancer in Chinese women with relatively high morbidity and mortality rates, seriously threatening the physical health and life safety of the patients. Currently, radical hysterectomy and pelvic lymph node dissection are the main methods for treating cervical cancer. According to clinical reports, the prognostic effect of simple radical resection in stage IB2-IIB cervical cancer is still far from satisfactory, and the risks of postoperative nodal metastasis and infiltration are raised remarkably [1,2]. Neoadjuvant chemotherapy is a kind of adjunctive medical therapy for malignant tumors. In a new version of guidelines for the diagnosis and treatment of cervical cancer published by the In-

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ternational Federation of Gynecology and Obstetrics (FIGO), it is recommended that neoadjuvant chemotherapy can be applied before radical hysterectomy [3]. In addition, the findings of many studies in China and foreign countries have manifested that neoadjuvant chemotherapy exerts prominent effects in improving the success rate of surgery and extending the survival of cervical cancer patients [4,5]. In this research, the influence of neoadjuvant chemotherapy on the efficacy, clinical indicators, prognosis and neutrophil/lymphocyte ratio (NLR) of stage IB2-IIB cervical cancer were investigated.

Methods

General data

A total of 120 patients with cervical cancer admitted to and treated in our hospital from January 2014 to May 2016 were selected as the study subjects. This research was approved by the Ethics Committee of our hospital, and the patients and their families were informed of and signed the informed consent.

Inclusion criteria: patients definitely diagnosed with cervical cancer through cytological and pathological examinations, those with FIGO stage of IB2-IIB, age >20 years and a Karnofski performance status (KPS) score >60 points, those who had no history of radiotherapy or chemotherapy, those who underwent radical hysterectomy and pelvic lymph node dissection after chemotherapy, those with basically normal hepatic, renal and cardiac function, and those who could accept follow-up.

Exclusion criteria: patients complicated with other pelvic diseases, malignant tumors, fever, severe infections, drug allergy or incompatibility, apparent bone marrow depression or mental diseases.

The 120 cervical cancer patients enrolled were divided into the control group (n=60) and the observation group (n=60) using a random number table. The clinical data such as age, pathological type, pathological stage and grade of differentiation had no statistically significant differences between the two groups (p>0.05), which were comparable (Table 1).

Therapeutic methods

Neoadjuvant chemotherapy combined with surgery was adopted for the observation group, in which the chemotherapy regimens were as follows: TP regimen: cisplatin (70-80 mg/m^2) + paclitaxel (150-175 mg/m^2), TC regimen: carboplatin (AUC=5) + paclitaxel (150-175 mg/m^2) and TN regimen: nedaplatin (70-80 mg/m^2) + paclitaxel (150-175 mg/m^2). Dexamethasone was administered before chemotherapy to prevent stress responses, and the corresponding symptomatic therapies were applied according to clinical adverse events during chemotherapy once every 3 weeks for 1-3 courses of treatment. After the FIGO stage of the patients declined below IIB, and the lesions were decreased markedly at 2-3 after chemotherapy, radical hysterectomy and pelvic lymph node dissection were performed based on the comprehensive analysis of the patients' age, removal or preservation of ovaries and specific conditions during operation. Patients in the control group were directly subjected to radical hysterectomy and pelvic lymph node dissection.

Observation indexes

Tumor markers

Fasting peripheral venous blood (4 mL) was collected from the patients in the early morning before and after treatment, followed by centrifugation at 2,500 rpm for 15 min and harvesting of the supernatant. Then, enzyme-linked immunosorbent assay (ELISA) was employed to detect matrix metalloproteinase-9 (MMP-9), carcino-embryonic antigen (CEA) and cancer antigen 125 (CA-125) strictly according to the manufacturer's instructions of relevant kits provided by Roche (Basel, Switzerland).

Immune function indicators

A total of 4 mL of venous blood was collected from each patient, and the neutrophils, lymphocytes and T-lymphocyte subsets [cluster of differentiation (CD) 4$^+$ and CD8$^+$] in the serum were measured using Attune®NxT Acoustic Focusing Cytometer (Thermo Fisher Scientific, Waltham, MA, USA), so as to calculate the NLR and CD4$^+$/CD8$^+$ ratio. The levels of serum immunoglobulin A (IgA) and IgM were determined via immune turbidimetry.

Quality of life and degree of cancer-related fatigue

The quality of life was evaluated by means of World Health Organization Quality of Life Scale Brief (WHOQOL-BREF) before and after treatment [6], which

Table 1. Comparisons of clinical data between the two groups

Group	*n*	*Age (years)*	*Pathological type (n)*			*FIHO stage (n)*			*Differentiation degree (n)*		
			Squamous cell carcinoma	*Adenocarcinoma*	*Squamous adenocarcinoma*	*Stage IB2*	*Stage IIA*	*Stage IIB*	*G1*	*G2*	*G3*
Control group	60	47.78±4.86	42	16	2	23	21	16	12	27	21
Observation group	60	48.23±5.15	45	14	1	24	22	14	14	26	20
t/Z		t=0.492	Z=0.513	Z=0.121	Z=0.138						
p		0.623	0.474	0.728	0.710						

included individual physiological health, mental status, independent ability, social relation and relation with surrounding environment, with a total score of 100 points. The higher score indicates a better quality of life. The degree of cancer-related fatigue was assessed by Cancer Fatigue Scale (CFS) [7] composed of 3 dimensions, namely body, emotion and cognition, of individuals, with a total score of 60 points, where the higher the score, the severer the cancer-related fatigue of the patients.

Response evaluation

By reference to RECIST [8], the response evaluation criteria are as follows: Complete response (CR): The tumor foci disappear after treatment, and the tumor indicators return to normal levels for over 4 weeks. Partial response (PR): The tumor indicators are improved evidently, and the size of tumor foci is decreased by 50% for more than 4 weeks. Stable disease (SD): The size of tumor foci is decreased or increased by less than 25%, without new lesions. Progressive disease (PD): The size of tumor foci is increased by over 25%, or new lesions occur. The effective rates (CR+PR) in the two groups were recorded and compared.

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was employed for data processing and analysis. The measurement data were expressed as x±s, and *t*-test was used. The enumeration data were presented as cases (n) or ratios (%), and x^2 test or Z-test were utilized. P<0.05 suggested that the difference was statistically significant.

Results

Changes in tumor markers before and after treatment in the two groups

There were no statistically significant differences in the levels of serum MMP-9, CEA and CA-125 between the two groups before treatment (p>0.05), but they declined in both groups after treatment (p<0.05), and the observation group had lower levels of MMP-9, CEA and CA-125 than the control group after treatment (p<0.05) (Table 2).

Changes in NLR and Igs before and after treatment in the two groups

The differences in the NLR, IgA and IgM levels were not statistically significant between the two groups before treatment (p>0.05). After treatment, however, those levels were decreased in both groups (p<0.05), and the decreases were greater in the observation group than those in the control group (p<0.05) (Table 3).

Changes in T-lymphocyte subsets before and after treatment in the two groups

The levels of $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ exhibited no statistically significant differences between the two groups before treatment (p>0.05), while they were decreased in the two groups after treatment (p<0.05), and the observation group had more

Table 2. Comparisons of changes in tumor markers before and after treatment between the two groups (n=60, x±s)

Group	*Time*	*MMP-9 (mg/L)*	*CEA (ng/mL)*	*CA-125 (U/mL)*
Control group	Before treatment	557.25±76.74	17.78±2.75	145.61±15.27
	After treatment	368.55±49.46	12.53±2.14	112.44±11.56
t/p intra-group comparison		15.861/<0.001	11.693/<0.001	12.987/<0.001
Observation group	Before treatment	549.87±77.55	18.26±2.59	143.78±16.31
	After treatment	201.67±38.88	9.78±1.96	70.78±10.13
t/p intra-group comparison		30.822/<0.001	20.223/<0.001	28.268/<0.001
t/p between groups after treatment		20.400/<0.001	7.340/<0.001	20.825/<0.001

Table 3. Comparisons of changes in NLR and Igs before and after treatment between the two groups (n=60, x±s)

Group	*Time*	*NLR*	*IgA (g/L)*	*IgM (g/L)*
Control group	Before treatment	2.13±0.43	3.88±0.42	1.71±0.24
	After treatment	1.87±0.33	2.76±0.33	1.32±0.22
t/p intra-group comparison		3.715/<0.001	16.242/<0.001	9.278/<0.001
Observation group	Before treatment	2.08±0.37	3.83±0.43	1.68±0.26
	After treatment	1.62±0.31	2.33±0.37	1.11±0.19
t/p intra-group comparison		7.381/<0.001	20.247/<0.001	13.711/<0.001
t/p between groups after treatment		4.276/<0.001	6.618/<0.001	5.595/<0.001

notable decreases than the control group (p<0.05) (Table 4).

Changes in quality of life and degree of cancer-related fatigue before and after treatment in the two groups

No statistically significant differences in the WHOQOL-BREF and CFS scores were detected between the two groups before treatment (p>0.05), but the WHOQOL-BREF score was raised, while that of CFS score was lowered in the two groups after treatment (p<0.05). The observation group displayed a higher WHOQOL-BREF score and a lower CFS score than the control group after treatment (p<0.05) (Table 5).

Disease control in the two groups

The effective rate in the observation group [71.67% (43/60)] was obviously higher than that in the control group [53.33% (32/60)], showing a statistically significant difference (p<0.05) (Table 6).

Pathological findings after operation in the two groups

The incidence rates of adverse clinical pathological findings such as nodal metastasis, vascular

Table 4. Comparisons of changes in T-lymphocyte subsets before and after treatment between the two groups (n=60, x±s)

Group	*Time*	*CD4⁺*	*CD8⁺*	*CD4⁺/CD8⁺ ratio*
Control group	Before treatment	55.28±5.78	42.31±4.45	1.33±0.22
	After treatment	49.34±5.11	39.45±2.22	1.26±0.15
t/p intra-group comparison		5.964/<0.001	4.610/<0.001	2.036±0.043
Observation group	Before treatment	56.77±6.25	41.87±4.62	1.35±0.21
	After treatment	44.44±4.56	37.34±2.46	1.19±0.18
t/p intra-group comparison		12.345/<0.001	6.704/<0.001	4.481/<0.001
t/p between groups after treatment		5.542/<0.001	4.698/<0.001	2.314±0.022

Table 5. Comparisons of changes in quality of life and degree of cancer-related fatigue before and after treatment between the two groups (n=60, x±s)

Group	*WHOQOL-BREF score (point)*		*CFS score (point)*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*
Control group	58.17±5.75	69.45±6.67▾	40.78±4.26	31.23±4.12▾
Observation group	57.69±5.67	76.67±6.79▾	41.04±4.18	25.42±3.53▾
t	0.460	5.876	0.337	8.281
p	0.646	<0.001	0.736	<0.001

▾p<0.05 *vs.* before treatment

Table 6. Comparison of disease control between the two groups [n (%)]

Group	*n*	*CR*	*PR*	*SD*	*PD*	*Effective rate*
Control group	60	8 (13.33)	24 (40.00)	17 (28.33)	11 (18.33)	32 (53.33)
Observation group	60	13 (21.67)	30 (50.00)	9 (15.00)	8 (13.33)	43 (71.67)
Z or x^2		Z=4.355	x^2=4.302			
p		0.047	0.038			

Table 7. Comparison of pathological findings after operation between the two groups [n (%)]

Group	*n*	*Nodal metastasis*	*Vascular invasion*	*Parametrial invasion*	*Positive margin*
Control group	60	10 (16.67)	8 (13.33)	9 (15.00)	7 (11.67)
Observation group	60	2 (3.00)	1 (1.67)	2 (3.00)	1 (1.67)
x^2		5.926	5.886	4.904	4.821
p		0.014	0.015	0.027	0.028

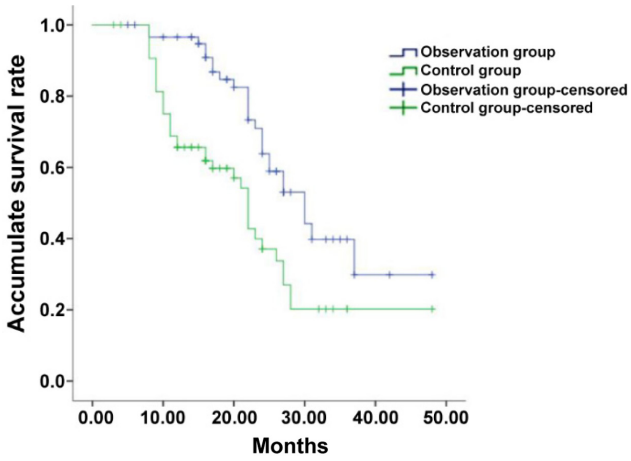

Figure 1. Comparison of 3-year survival between the two groups. The difference was statistically significant (p<0.05).

invasion, parametrial invasion and positive margin after operation were reduced distinctly in the observation group compared with those in the control group, with statistically significant differences (p<0.05) (Table 7).

Survival at 3 years after operation in the two groups

According to the follow-up results, the mean survival time in the observation group was remarkably longer than that in the control group [(29.79±3.58) months *vs.* (23.45±3.24) months], and the difference was statistically significant (p<0.05) (Figure 1).

Discussion

Both radical hysterectomy and pelvic lymph node dissection are major methods for the treatment of cervical cancer in the clinic, but it is usually difficult to directly excise the cancer lesion due to the large size, wide local infiltration and other features of stage IB2-IIB cervical cancer. Clinical studies have manifested that preoperative chemotherapy can create favorable conditions for subsequent surgical treatments. Chemotherapy is able to effectively kill the tumor foci and invisible metastatic cells, decrease the volume of tumor foci and infiltration range, lower the tumor grade, mitigate intraoperative dissemination and postoperative metastasis and reduce the recurrence risk after operation, thus ameliorating the prognosis, improving the quality of life and prolonging the survival of the patients [9,10]. Neoadjuvant chemotherapy has been extensively applied in clinical departments so far. A relevant study [11] demonstrated that the control rate of cervical cancer is increased markedly, and the middle- and long-term survival time of the patients is extended after neoadjuvant chemotherapy. In this research, TP, TC and TN regimens of neoadjuvant chemotherapy combined with surgical resection were conducted according to the clinical practical situations of the patients, and the results indicated that the patients in the observation group had a higher clinical effective rate and longer postoperative survival than those in the control group (p<0.05), which are consistent with the aforementioned findings. The results in this research suggest that neoadjuvant chemotherapy can produce desirable prognosis and efficacy in stage IB2-IIB cervical cancer.

As a member of the MMPs family, MMP-9 is closely correlated with the signal transduction among cells and between cells and extracellular matrix as well as the related actions. It can destroy the histological barrier of tumor cell invasion by degrading various protein components in the extracellular matrix of tumor, thereby playing key roles in tumor invasion and metastasis [12]. CEA is a broad-spectrum cancer marker which can reflect the presence of multiple cancers and serve as an important marker of efficacy judgment, disease progression and prognosis evaluation of cancer [13]. CA-125, a type of glycoprotein derived from the coelomic epithelial tissues during embryonic development, does not exist in normal tissues but has high expressions in the serum of patients with cervical cancer, endometrial cancer, ovarian cancer, breast cancer, etc., so it is a cancer-specific marker [14]. The levels of serum MMP-9, CEA and CA-125 in the observation group were decreased compared with those in the control group after treatment (p<0.05), suggesting that neoadjuvant chemotherapy can prominently down-regulate the expression levels of markers such as MMP-9, CEA and CA-125 in the serum of cervical cancer patients.

Neutrophils and lymphocytes are two kinds of leukocytes that are crucial components in cervical cancer cells. Lymphocytes can specifically recognize and eliminate cancer cells and simultaneously secret a series of immunologic factors to activate autoimmune reaction in the body, and reduction in lymphocytes indicates abnormal immune function, accelerating the growth of cancer cells [15]. Previous studies have elaborated that NLR has close associations with the therapeutic effect and prognosis of diversified cancers. Besides, NLR can reflect the inflammatory and immune status in cancer patients, acting as one of the vital prognostic indicators [16]. It was shown in this research that the observation group had a lower NLR than the control group after treatment (p<0.05), implying that neoadjuvant chemotherapy is capable of decreasing NLR in stage IB2-IIB cervical cancer. In addition, the comparisons of levels of T-lymphocyte

subsets, IgA and IgM after treatment between the two groups manifested that neoadjuvant chemotherapy affected the cellular immune state in the patients, leading to immunodepression. Therefore, related treatments that improve the immunity can be taken into consideration, so as to enhance the clinical prognosis and efficacy [17,18].

According to clinical studies, decreasing the incidence and degree of cancer-related fatigue of cancer patients is conducive to prognosis and rehabilitation as well as improvement of later quality of life [19,20]. In this research, the CFS score was lower, but the WHOQOL-BREF score was higher in the observation group than those in the control group after treatment ($p<0.05$), indicating that neoadjuvant chemotherapy is able to reduce the degree of cancer-related fatigue and improve the quality of life of cervical cancer patients. Moreover, the results in this research displayed that the incidence rates of adverse clinical pathological findings such as lymph node metastasis, vascular invasion, parametrial invasion and positive margin after operation declined notably in the observation group in comparison with those in the control group ($p<0.05$), suggesting that neoadjuvant chemotherapy is beneficial to relieving the occurrence of postoperative nodal metastasis and tissue invasion, thus strengthening the prognostic effect and extending the survival of the patients.

Conclusions

In conclusion, neoadjuvant chemotherapy can effectively decrease the content of tumor markers in the serum, NLR, metastasis rate of cancer cells and degree of cancer-related fatigue, improve the quality of life, prolong the survival and produce satisfying clinical efficacy. Nevertheless, it has certain inhibitory effects on patient's immune function at the same time. Hence, neoadjuvant chemotherapy can be applied in combination with therapies ameliorating the immune function in clinical treatments.

Conflict of interests

The authors declare no conflict of interests.

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