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ORIGINAL RESEARCH

Effects of Sintilimab Plus Radiotherapy on Levels of Spondin-2 and Glucose Transporter-1 in Patients with Cervical Cancer

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Purpose: We aimed to evaluate the effects of sintilimab plus radiotherapy on levels of Spondin-2 and glucose transporter-1 (Glut-1) in patients with cervical cancer.

Patients and Methods: A total of 112 patients with cervical cancer treated from January 2019 to January 2021 were selected in this randomized control trial and divided into a control group (n = 56) and a study group (n = 56) using the random number table method. Chemotherapy using docetaxel + cisplatin was performed for both groups, based on which the control group was given radiotherapy (external conformal radiotherapy + intracavitary irradiation), and the study group received sintilimab plus radiotherapy. The treatment lasted for six cycles, with 21 days as one cycle.

Results: The total response rate of the study group was higher than that of the control group (55.36% vs 33.93%) ($P < 0.05$). There were no significant differences in adverse effects between the two groups ($P > 0.05$). After six cycles of treatment, the levels of carcinoembryonic antigen, squamous cell carcinoma antigen, vascular endothelial growth factor-A, vascular endothelial growth factor receptor 2, Spondin-2 and Glut-1 decreased in both groups compared with those before treatment, and they were lower in the study group ($P < 0.05$). The survival rate of the study group was higher than that of the control group (87.50% vs 71.43%) ($P < 0.05$).

Conclusion: Sintilimab plus radiotherapy can effectively reduce the levels of serum tumor markers, such as Spondin-2 and Glut-1, and enhance the clinical efficacy on patients with cervical cancer, without increasing adverse effects.

Keywords: cervical cancer, glucose transporter-1, radiotherapy, sintilimab, spondin-2

Introduction

Most patients with cervical cancer may have no symptoms at the early stage, but abnormal vaginal bleeding, contact bleeding and other symptoms may occur with the progression of the disease. Therefore, most patients have been in the mid-late stage upon diagnosis.[1,2] Using high-energy rays for local tumor treatment, radiotherapy is commonly used to treat middle-stage and advanced cervical cancer, which can directly or indirectly kill cancer cells and control tumor growth.[3] However, radiotherapy still has an unsatisfactory effect on some patients, and it causes adverse effects such as nausea, vomiting and skin damage, so it is still necessary to explore other clinical treatment methods.

Sintilimab is a fully human monoclonal antibody targeting programmed cell death receptor-1 (PD-1), which can block the PD-1/programmed death ligand 1 (PD-L1) pathway and activate the antitumor activity of lymphocytes, exerting a sustained antitumor effect.[4] Spondin-2, a secreted extracellular matrix protein, participates in many important cell activities such as neuron growth and development and plays an important role in specific and non-specific immune responses. The increase of Spondin-2 level has been closely associated with a variety of malignancies.[5] Besides, glucose transporter-1 (Glut-1) is the downstream target gene of hypoxia-inducible factor 1, which plays a crucial role in glycolysis in cells. The elevation of its level has also been associated with the occurrence and metastasis of many malignancies.[6]

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Therefore, sintilimab plus radiotherapy was applied to patients with cervical cancer in this study, and its effects on the levels of Spondin-2 and Glut-1 were observed, aiming to provide valuable clinical evidence for future treatment.

Materials and Methods

General Data

This study was approved by the ethics committee of Taizhou Hospital, Wenzhou Medical University (approval No. KL20240501), and performed following the guidelines outlined in the Declaration of Helsinki. Written informed consent was obtained from all the study participants. The sample size was determined according to the results of pre-experiment. A total of 112 patients with cervical cancer treated in our hospital from January 2019 to January 2021 were selected in this randomized control trial and divided into a control group (n = 56) and a study group (n = 56) using the random number table method.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients meeting the diagnostic criteria for cervical cancer,[7] and confirmed by cervical tissue biopsy, (2) those with normal liver and kidney functions, (3) those with an estimated survival period >3 months, and (4) those who had a good physical condition according to the Karnofsky Performance Status scale.[8]

The exclusion criteria involved: (1) patients complicated with uncontrolled hypertension (blood pressure above 140/90 mm Hg), (2) those receiving immunotherapy drugs or other targeted therapies, (3) those with contraindications to the drugs used in this study, (4) those complicated with hematological diseases or immune dysfunction, (5) those complicated with other malignancies, (6) those who were participating in clinical trials of other drugs, (7) pregnant or lactating women, (8) those complicated with disturbance of consciousness or cognitive impairment, or (9) those complicated with bone marrow reserve dysfunction.

Chemotherapy Method for Both Groups

Chemotherapy using docetaxel (Zhejiang Wansheng Pharmaceutical Co., Ltd., China; strength: 0.5 mL: 20 mg) + cisplatin (Qilu Pharmaceutical Co., Ltd., China; strength: 10 mg) was given to both groups. Specifically, 25 mg/m^2 docetaxel and 25 mg/m^2 cisplatin were intravenously infused for 30–60 min on D1-D3, and the treatment lasted for six cycles, with 21 d as one cycle.

Method for Control Group

In addition to chemotherapy, external conformal radiotherapy and intracavitary irradiation were conducted for the control group. First, external conformal radiotherapy (6 MV X-ray) was performed 5 times a week, with the vagina, parametrial tissue, uterine body and lymphatic drainage region as clinical target volume (CTV), and the area outward expanded by 7 mm from CTV as planning target volume (PTV). The dose was 6160 cGy/28f (2.2 Gy/f) in PTV of metastatic lymph nodes and 5040 cGy/28f (1.8 Gy/f) in CTV. Then intracavitary irradiation was performed with a multileaf collimator [4× (10–17) cm] at 6Gy/f (6 f, 36 Gy in total).

Method for Study Group

On the basis of chemotherapy and the treatment method for the control group, sintilimab [Xinda Biopharmaceutical (Suzhou) Co., Ltd., China; strength: 10 mL: 100 mg] was also used for the study group. Specifically, 200 mg of sintilimab diluted in 100 mL of 0.9% sterile normal saline was intravenously infused for 30–60 min on D1, and the treatment lasted for six cycles, with 21 d as one cycle.

Observation Indicators

(1) Clinical efficacy:[9] The clinical efficacy was evaluated by CT scan for both groups after all treatment. Complete response was defined as complete disappearance of tumor lesions for more than 4 weeks. Partial response was defined as a reduction of tumor lesion areas >30% for more than 4 weeks. A reduction of tumor lesion areas ≤30% and no new

lesions within 4 weeks were considered stable disease. An increase in tumor lesion areas >20% or emergence of new lesions was considered progressive disease. The total response rate was calculated: complete response rate + partial response rate.

(2) Adverse effects: The incidence rates of nausea and vomiting, liver and kidney dysfunction, bone marrow suppression and rash were recorded during treatment.

(3) Serum tumor markers: Before treatment and after six cycles of treatment, 3 mL of fasting venous blood was drawn from each patient, and centrifuged at 3500 r/min with a centrifugal radius of 8 cm for 15 min to separate the serum. Then the levels of carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), vascular endothelial growth factor-A (VEGF-A) and vascular endothelial growth factor receptor 2 (VEGFR2) were measured by enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions of kits provided by Wuhan CUSABIO Co., Ltd. (China) and Shanghai Jining Biological Preparation Co., Ltd. (China).

(4) Levels of Spondin-2 and Glut-1: The levels of serum Spondin-2 and Glut-1 were measured by ELISA before treatment and after six cycles of treatment.

(5) Survival status: All patients were followed up by outpatient visit or telephone calls for 18 months to record their survival status.

Statistical Analysis

The SPSS 23.0 software was used for statistical analysis. The measurement data were described by mean ± standard deviation ($\bar{x} \pm s$) and compared with the *t*-test. The count data were represented as percentage [n (%)] and examined by the χ^2 test. The rank sum test was performed for ranked data. Kaplan–Meier survival curves were plotted. $P < 0.05$ was considered statistically significant.

Results

The baseline clinical data were comparable between the two groups ($P > 0.05$) (Table 1). The total response rate of the study group was higher than that of the control group ($P < 0.05$) (Table 2).

There were no significant differences in adverse effects between the two groups ($P > 0.05$) (Table 3).

Before treatment, no significant differences were found in the levels of serum tumor markers between the two groups ($P > 0.05$). After six cycles of treatment, the levels of CEA, SCC-Ag, VEGF-A and VEGFR2 declined in both groups compared with those before treatment, and they were lower in the study group than those in the control group ($P < 0.05$) (Table 4).

Table 1 Baseline Clinical Data

Data		Control Group (n=56)	Study Group (n=56)	χ^2/t	P
Age (year)		50.63±5.62	50.31±6.17	1.899	0.168
Body mass index (kg/m^2)		25.37±2.16	25.29±2.24	1.746	0.186
White blood cell count (×10^9/L)		3.28±1.02	3.23±0.98	0.846	0.400
Hemoglobin level (g/L)		116.28±12.39	114.76±13.52	1.089	0.279
Platelet count (×10^9/L)		197.63±41.26	199.18±40.27	0.498	0.620
Pathological type [n (%)]	Squamous cell carcinoma	31 (55.36)	33 (58.93)	6.723	0.010
	Adenocarcinoma	25 (44.64)	23 (41.07)		
Pathological stage [n (%)]	IB	8 (14.29)	6 (10.72)	1.102	0.576
	IIA	11 (19.64)	11 (19.64)		
	IIB	13 (23.21)	15 (26.79)		
	III	18 (32.14)	19 (33.92)		
	IVA	6 (10.72)	5 (8.93)		

Table 2 Clinical Efficacy [n (%)]

Group	Complete Response	Partial Response	Stable Disease	Progressive Disease	Total Response Rate
Study (n=56)	7 (12.50)	24 (42.86)	16 (28.57)	9 (16.07)	31 (55.36)
Control (n=56)	2 (3.57)	17 (30.36)	21 (37.50)	16 (28.57)	19 (33.93)
Z/χ^2	Z=2.480				χ^2=5.203
P	0.013				0.023

Table 3 Adverse Effects [n (%)]

Group	Nausea and Vomiting	Liver and Kidney Dysfunction	Bone Marrow Suppression	Rash
Study (n=56)	24 (42.86)	12 (21.43)	32 (57.14)	16 (28.57)
Control (n=56)	21 (37.50)	13 (23.21)	29 (51.79)	14 (25.00)
χ^2	0.334	0.052	0.324	0.182
P	0.563	0.821	0.569	0.670

Table 4 Levels of Serum Tumor Markers Before and After Six Cycles of Treatment ($\bar{x} \pm s$)

Group	CEA (μg/L)		SCC-Ag (μg/L)		VEGF-A (ng/L)		VEGFR2 (ng/L)	
	Before Treatment	After Six Cycles of Treatment	Before Treatment	After six Cycles of Treatment	Before Treatment	After Six Cycles of Treatment	Before Treatment	After Six Cycles of Treatment
Study (n=56)	8.18±1.96	2.62±0.71[a]	13.76±2.83	2.28±0.65[a]	798.63±136.28	576.40±118.63[a]	440.94±88.72	296.58±76.52[a]
Control (n=56)	8.24±2.12	3.59±0.94[a]	13.92±2.79	3.46±0.78[a]	801.43±142.76	639.75±126.43[a]	438.21±91.17	339.72±80.28[a]
t	0.156	6.162	0.301	8.697	0.106	2.734	0.161	2.911
P	0.877	<0.001	0.764	<0.001	0.916	0.007	0.873	0.004

Note: [a]P<0.05 vs the same group before treatment.

Before treatment, no significant differences were found in the levels of Spondin-2 and Glut-1 between the two groups (P > 0.05). After six cycles of treatment, the levels of Spondin-2 and Glut-1 declined in both groups compared with those before treatment, and they were lower in the study group than those in the control group (P < 0.05) (Table 5).

The 18-month follow-up results showed that the survival rate of the study group was higher than that of the control group (P < 0.05) (Table 6). The survival curves of patients with cervical cancer after treatment are shown in Figure 1.

Table 5 Levels of Spondin-2 and Glut-1 Before Treatment and After Six Cycles of Treatment ($\bar{x} \pm s$)

Group	Spondin-2 (μg/L)		Glut-1 (μmol/L)	
	Before Treatment	After Six Cycles of Treatment	Before Treatment	After Six Cycles of Treatment
Study (n=56)	25.13±7.32	12.83±3.17[b]	256.39±25.73	188.59±21.74[b]
Control (n=56)	24.86±7.75	15.76±3.29[b]	258.31±26.58	202.63±22.32[b]
t	0.190	4.799	0.388	3.372
P	0.850	<0.001	0.699	0.001

Note: [b]P<0.05 vs the same group before treatment.

Table 6 Survival Status [n (%)]

Group	Survived	Died
Study (n=56)	49 (87.50)	7 (12.50)
Control (n=56)	40 (71.43)	16 (28.57)
χ^2	4.432	
P	0.035	

Discussion

Cervical cancer frequently occurs in people with low immunity, multiple pregnancies and births, and premature sexual life, with high morbidity and mortality rates.[10] Surgery is an important means for the clinical treatment of cervical cancer, which can directly remove the lesion tissues. However, residual tumor tissues can be found after surgery, and tumor cells may further metastasize and spread if no effective treatment is conducted, resulting in adverse consequences.[11] Radiotherapy is also one of the important treatment means for cervical cancer, which can effectively inhibit the proliferation and reduce the activity of cancer cells using high-energy rays. Regular radiotherapy can effectively control tumor growth and prevent cancer cell metastasis.[12] The distant metastasis of cancer cells in some patients with advanced cervical cancer causes systemic pain, in which case radiotherapy can relieve patients' pain and prolong the survival time.[13] However, the lesion tissues in some patients have poor sensitivity to radioactive elements, so the therapeutic effect is unsatisfactory.

The occurrence and development of cervical cancer have been closely related to tumor immune escape.[14] During immune responses, a dual-signal system needs to be identified to stimulate T cell activation. The first signal is generated by the binding of T cell surface receptors to antigenic peptide-major histocompatibility

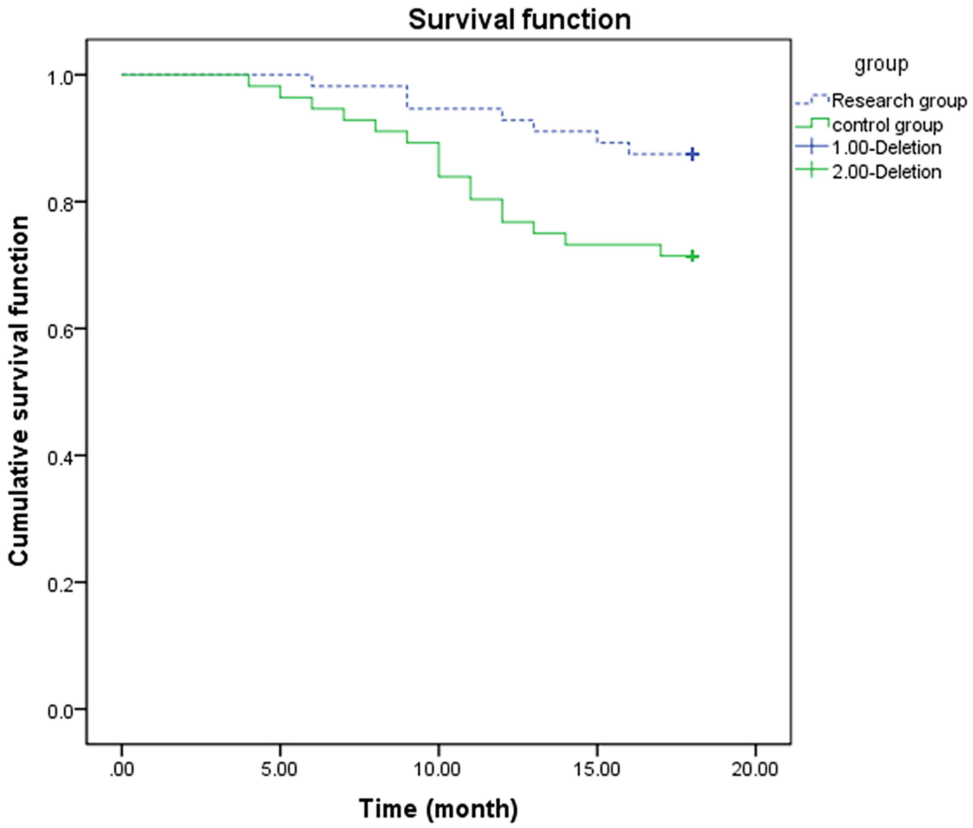

Figure 1 Survival curves of patients with cervical cancer after treatment.

complex, and the second signal is generated by the interaction of T cell surface costimulatory molecules with antigen-presenting cells. PD-1/PD-L1 can block the formation of stable contact between antigen-presenting dendritic cells and T cells. As a result, antigen-presenting cells cannot effectively transmit antigen information to cytotoxic lymphocytes, thus interfering with T cell activation and mediating the immune escape of tumor cells.[15,16] The expression of PD-1/PD-L1 in cancer tissues and peripheral blood of patients with cervical cancer rises compared with that in healthy people, weakening the tumor cell-killing ability of cytotoxic lymphocytes. Down-regulating the expression of PD-1/PD-L1 can suppress the migration and invasion of cervical cancer cells. Thus, the PD-1/PD-L1 pathway plays an important role in the occurrence and development of cervical cancer.[17] Sintilimab, a PD-1 monoclonal antibody, is characterized by a higher affinity than those of nivolumab and pembrolizumab, a stable and persistent receptor occupancy (>95%) and ability to induce strong antitumor immune responses.[18,19]

CEA and SCC-Ag are closely related to the occurrence and development of tumors and can reflect the changes in disease conditions. VEGF-A is an angiogenic factor, and VEGF-A/VEGFR2 signaling regulates the survival, proliferation and migration of vascular endothelial cells, playing an important role in cardiovascular diseases and participating in tumor growth and invasion. In this study, after six cycles of treatment, the levels of CEA, SCC-Ag, VEGF-A and VEGFR2 were lower and the total response rate was higher in the study group than those in the control group, suggesting that the combination therapy can reduce the levels of serum tumor markers and improve the clinical efficacy. The possible reasons are as follows. First, after entering the human body, sintilimab can bind PD-1 on the surface of T cells to hinder PD-1 from binding PD-L1, so T cells can work normally, regain costimulatory signals, and recover the tumor cell-killing ability. Second, sintilimab plus radiotherapy can control tumor growth through different mechanisms and synergize in the treatment of cervical cancer, thus enhancing the clinical efficacy.

Spondin-2 has a significantly higher expression in gastric cancer tissues than in adjacent tissues, which can promote cancer cell growth and metastasis through the P13K/AKT signaling pathway.[20] The serum Spondin-2 level is considered a marker for lung cancer, prostate cancer and renal cancer, and the down-regulation of Spondin-2 can significantly suppress cancer cell proliferation and invasion.[21] Glut-1 has almost no expression in para-carcinoma epithelial cells and normal epithelial cells but has a significantly increased expression in gastric cancer, colon cancer, non-small cell lung cancer and cervical cancer issues, which can increase the glucose level in tumor cells and participate in tumor formation, metastasis and invasion.[22,23] In this study, the study group had lower levels of serum Spondin-2 and Glut-1 and a higher survival rate than those of the control group after six cycles of treatment, demonstrating that sintilimab plus radiotherapy can effectively lower the levels of Spondin-2 and Glut-1 and raise the survival rate of patients. Probably, radiotherapy can directly kill tumor cells, and sintilimab can restore the ability of T cells to recognize and kill tumor cells, enhance the antitumor immune effect and reduce the death risk. In addition, there were no significant differences in adverse effects between study and control groups, proving that the combination therapy did not increase the incidence rate of adverse effects.

Nevertheless, this study is limited. The study is based on a relatively small simple cohort in a single center, so the plausibility and credibility of the presented data need to be validated in a larger multicenter cohort.

Conclusion

In conclusion, sintilimab plus radiotherapy can effectively reduce the levels of serum tumor markers, Spondin-2 and Glut-1, and enhance the clinical efficacy of patients with cervical cancer, without increasing adverse effects.

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Disclosure

The authors declare no conflicts of interest in this work.

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