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Original Article

Efficacy and safety of Camrelizumab combined with Abraxane + lobaplatin regimen for advanced gastric cancer

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Abstract: Purpose: To examine the safety and effectiveness of the combination of Camrelizumab and Abraxane + lobaplatin in advanced gastric cancer therapy. Methods: The data of 60 patients with advanced gastric cancer in Shaanxi Provincial People's Hospital from May 2017 to March 2019 were analyzed retrospectively. The patients were divided into a study group (n=30) and a control group (n=30) according to different treatment methods. The study group received Camrelizumab combined with the Abraxane + lobaplatin regimen, and the control group received the Abraxane + lobaplatin regimen only. The levels of soluble interleukin-2 receptor (sIL-2R), secretory glycoprotein (Dickkopf-1, DKK-1) and tumor specific growth factors (TSGFs), the relative molecular expression of serum miRNA-1290, miRNA-647 and miRNA-182, and the Karnofsky performance status (KPS) were compared between the two groups. The adverse reactions of the two groups were observed, and the 3-year survival rates were compared. Results: The disease control rate and overall remission rate of the study group (53.33%, 90.00%) were higher than those of the control group (26.67%, 50.00%), with statistically significant differences (P<0.05). The levels of sLL-2R, DKK-1 and TSGF were reduced in both groups (*P<0.*05) after being treated, whereas these were comparatively lower levels in the study group (P<0.05). After treatment, serum concentration of miRNA-1290, miRNA-647 and miRNA-182 were lower in the study group than in the control group (*P<0.*05). Upon comparison with those in the control group, the KPS scores were higher at 1, 3 and 6 months after treatment in the study group (*P<0.*05). The incidence of adverse events was not significantly different between the two groups (P>0.05). The 1-year, 2-year and 3-year survival rates were higher in the study group (57.38%, 39.34% and 29.51%) than in the control group (32.79%, 18.03% and 8.20%) (*P<0.*05). Conclusion: The combination of Camrelizumab and Abraxane + lobaplatin is an effective treatment for advanced gastric cancer and can increase the patient's survival rate.

Keywords: Abraxane, Camrelizumab, advanced gastric cancer, efficacy, safety

Introduction

Gastric cancer is second only to lung cancer in China in terms of incidence, and the initial symptoms are insidious. Most patients with gastric cancer are diagnosed when the disease has advanced. Surgical resection is adequate, but it is easy to have distant metastasis and recurrence after the operation, and the long-term curative efficacy in patients is not good. Fluorouracil and platinum-based essential chemotherapy is mostly used in the clinical treatment of gastric cancer. However, systemic chemotherapy can only improve patients' symptoms and quality of life, with difficulty in improving patients' survival rates [1]. With the increasing variety of drugs, the choice of clinical treatment options is more diversified, so the selection of treatment schemes with promising efficacy and safety among many treatment schemes has become the focus of clinicians. Abraxane is a broad-spectrum paclitaxel-based chemotherapy agent, which is a third-generation paclitaxel. Compared with ordinary paclitaxel, it has high distribution in tumor tissues, high efficacy and low toxicity. It is a conventional chemotherapy drug [2]. Besides, the progress of immunotherapy has made anti-PD-1 a novel treatment for malignant tumors. Immunotherapy can mobilize the body's immune func-

Table 1. Comparison of general data between the two groups [n (%), ($\overline{x}$ ± s)]

Group	Sex		Age	Tumor classification		Degree of differentiation		
	Male	Female		Adenocarcinoma	Others	Middle differentiation	Middle and low differentiation	Low differentiation
Study group (*n*=30)	19 (63.33)	11 (36.67)	56.43±9.62	3 (10.00)	27 (90.00)	7 (23.33)	13 (43.33)	10 (33.33)
Control group (*n*=30)	16 (53.33)	14 (46.67)	55.03±10.08	5 (16.67)	25 (83.33)	9 (30.00)	10 (33.33)	11 (36.67)
χ^2	0.617		0.550	-			0.689	
P	0.432		0.584	-			0.709	
Fisher exact probability value				0.706				

tion to discriminate cancer cells and enhance the body's ability to tolerate chemotherapy drugs. Several previous studies have reported the significant anti-tumor activity of Camrelizumab [3, 4]. Camrelizumab, a humanized immunoglobulin monoclonal antibody, can enhance the body's anti-tumor ability by targeted binding to programmed cell death protein-1 (PD-1) and blocking its binding to programmed hope protein ligand-1 (PD-L1) [5]. Albumin-bound paclitaxel can promote the apoptosis of tumor cells and increase the probability of immune response, and combined immunotherapy may improve treatment efficiency [6]. Paclitaxel combined with platinum can also prolong the survival time of patients [7]. Previous studies [8, 9] have applied Carrell monoclonal antibody and albumin paclitaxel, respectively or in combination, in the treatment of gastric cancer, but there is no recognized "best scheme" for the treatment of advanced gastric cancer. According to related studies [10], Camrelizumab combined with albumin paclitaxel/lobaplatin is effective and safe in treating locally advanced esophageal cancer. This study aimed to investigate the efficacy and safety of Camrelizumab combined with albumin Abraxane + carboplatin in the treatment of advanced gastric cancer and to provide data to support for the application of the new treatment regimen.

Data and methods

General information

The data of 60 patients with advanced gastric cancer in the Shaanxi Provincial People's Hospital from May 2017 to March 2019 were retrospectively analyzed. The patients were divided into a study group and a control group according to different treatment schemes, with 30 cases in each group. The study group comprised of 11 females and 19 males who were aged 37-81 years, with a mean age of 56.43±9.62 years. In this group, there were 3 cases of adenocarcinoma and 27 other cases; 7 cases of medium differentiation, 13 cases of medium-low differentiation and 10 cases of low differentiation. The control group was comprised of 14 females and 16 males with ages ranging from 40 to 78 years and a mean age of (55.03±10.08) years. There were 5 cases of adenocarcinoma and 25 other cases; 9 cases of medium differentiation, 10 cases of medium-low differentiation and 11 cases of low differentiation. After comparing the two data sets, they were found to be comparable (P>0.05), **Table 1**. The approval of the study was provided by the Ethics Committee of Shaanxi Provincial People's Hospital.

Inclusion criteria

① Patients were diagnosed for the first time and did not receive anti-tumor therapy such as chemotherapy, radiotherapy and immunotherapy before being included in the study. ② Patients were between 18 and 80 years old. ③ Patients were diagnosed with advanced gastric cancer by clinicopathological and imaging examinations [11]. ④ Patients had an estimated survival time of more than 3 months. ⑤ Patients were at IV stage in TNM staging. ⑥ Patients had a good heart, liver, lung, kidney and bone marrow reserve functions.

Exclusion criteria

① Patients had other tumors, autoimmune diseases, hematologic diseases or digestive system diseases. ② Patients were diagnosed with advanced gastric cancer. ③ Patients were combined with cerebral infarction, myocardial infarction, or arterial and venous thrombosis. ④ Patients could not tolerate chemotherapy.

⑤ Patients had a treatment history by PD-L1, anti-PD-1, cytotoxic T-lymphocyte antigen-4 or other drugs. ⑥ Patients had hemorrhagic tendency. ⑦ Patients were allergic to the study drugs.

Methodology

Study group: The study group was given Camrelizumab (Suzhou Shengdiya Biomedical Co., Ltd., S20190027) 200 mg intravenous drip, once/3 weeks; Abraxane (Jiangsu Hengrui Pharmaceutical Co., Ltd., H20183378) 120 mg/m^2 intravenous infusion + Lopressor (Hainan Chang'an International Pharmaceutical Co., Ltd., H20080359) 35 mg/m^2 arterial infusion, 1 time/3 weeks, with 3 weeks as 1 chemotherapy cycle, for 6 cycles of treatment in total.

Control group: The Abraxane + Lopressor regimen was administered the same dosing criteria as the study group.

Observation indicators

① Clinical efficacy. ② Tumor markers in serum: Fasting venous blood (9 ml) was taken from both groups of patients, divided into 3 portions of 3 ml/serving, two of which were centrifuged for 5 min at 3000 r/min followed by the extraction of the upper serum layer and cryopreservation for measurement. One serum specimen was taken and subjected to measure the levels of soluble interleukin-2 receptor (sIL-2R), Dickkopf-1 (DKK-1) and tumor specific growth factors (TSGFs) using Enzyme-linked immunosorbent assay. SIL-2R kits were purchased from Shanghai Jianglai Biotechnology Co., Ltd., batch number: 1532208294. DKK-1 kits were purchased from Wuhan Elite Biotechnology Co., Ltd., batch number: E-EL-H0057c. TSGF kits were purchased from Beijing Yaanda Biotechnology Co., Ltd., batch number: YAD1691s. ③ The miRNA levels in serum: 1 ml of TRIzol extractant was added to a serum specimen for total RNA extraction and examination. The extracted total RNA was transcribed by qRT-PCR reverse transcription kits. RNA was diluted to 2 ng/ul with water, then RT solution was added. PCR reaction was performed at 16°C for 60 min, 42°C for 30 min and 85°C for 10 min, and the cDNA obtained by reverse transcription was cooled and diluted, then stored at -20°C. Two ul cDNA samples were used as PCR quantitative detection templates for PCR reaction. PCR amplification followed the conditions 95°C pre-denaturation for 3 min, 95°C denaturation for 5 s, extension at 61°C for 30 s, 35 cycles.

The forward and reverse primers for miRNA-1290 were 5'-ACACTCCAGCTGGGTGGATTTTTGGA-3' and 5'-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGTCCCTGA-3', respectively. The forward and reverse primers for miRNA-182 were 5'-TGCGGTTTGGCAATGGTAGAAC-3' and 5'-CCAGTGCAGGGTCCGAGGT-3', respectively. The forward and reverse primers for internal reference U6 were 5'-GCGCGTCGTGAAGCGTTC-3' and 5'-GTGCAGGGTCCGAGGT-3', respectively. The relative molecular expressions of miRNA-1290, miRNA-647 and miRNA-182 in serum were calculated by $2^{-\Delta\Delta Ct}$. ④ Quality of life: The quality of life was assessed before treatment, and after 1, 3 and 6 months of treatment using the Karnofsky performance status (KPS) [11] for tumor patients. KPS is scored from 0 to 100 points, and higher quality of life is indicated by higher scores. ⑤ Adverse reactions: Evaluation of adverse reactions was conducted using the Common Adverse Events Evaluation Criteria developed by the US Department of Health and Human Services [12]. ⑥ Survival rate: The survival time was recorded in both groups during the 3 years of follow-up, with one visit to the hospital at 3 and 6 months after discharge, and one telephone follow-up every 6 months afterwards.

Efficacy assessment criteria

The evaluation of the efficacy of the two groups was carried out according to response evaluation criteria in solid tumors RECISTI.1 [13]. The efficacy was divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). CR: the patient's lesions completely disappeared with less than 10 mm of short axis value of all metastatic lymph nodes. PR: the patient's lesion diameter shortened by more than 30% compared with that before treatment; SD: the lesion diameter did not meet the criteria of PR and PD. PD: taking the minimum diameter of the sum of lesion diameters as a reference, the sum of lesion diameters increased by more than 20% compared with that before treatment, and the

Table 2. Comparison of clinical efficacy between the two groups [cases (%)]

Group	CR	PR	SD	PD	ORR	DCR
Study group (n=30)	0 (0.00)	16 (53.33)	11 (36.67)	3 (10.00)	16 (53.33)	27 (90.00)
Control group (n=30)	0 (0.00)	8 (26.67)	7 (23.33)	15 (50.00)	8 (26.67)	15 (50.00)
χ^2 Value					4.444	11.429
P-value					0.035	0.001

Note: Complete Remission (CR), Partial Remission (PR), Stable Disease (SD), and Progressive Disease (PD), Disease Control Rate (DCR), Overall Remission Rate (ORR).

Table 3. Comparison of soluble interleukin-2 receptor (sLL-2R), Dickkopf-1 (DKK-1) and tumor specific growth factors (TSGF) levels in serum between the two groups ($\bar{x} \pm s$)

Group	sLL-2R (U/L)		DKK-1 (pg/ml)		TSGF (IU/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n=30)	990.45±96.53	355.47±100.33[a]	78.07±9.23	30.36±9.19[a]	82.19±6.87	36.86±3.15[a]
Control group (n=30)	984.72±76.75	498.03±50.56[a]	75.36±8.63	52.13±9.35[a]	83.11±6.64	59.25±6.09[a]
t-value	0.254	6.950	1.174	9.093	0.528	17.895
P-value	0.800	<0.001	0.245	<0.001	0.600	<0.001

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

absolute value of the increase was 5 mm or more or new lesions appeared. Disease control rate = CR+PR+SD, and overall remission rate = CR+PR.

Statistical methods

Analysis and processing of all study data were carried out using the statistical software SPSS 24.0. The measurement data were presented as mean ± SD ($\bar{x} \pm s$), and when the normal distribution and variance were equal, t-test was used. The counting data were described by n and %, and the disordered classification data passed (χ^2-test or Fisher exact probability). Kaplan-Meier method was used to draw survival curve, and logarithmic rank test was used to compare the survival distributions. A difference was considered to be statistically significant when P<0.05.

Results

Comparison of general data

There was no significant difference in general data between the two groups (P>0.05).

Comparison of clinical efficacy between the two groups

The disease control rate and overall remission rate were higher in the study group (53.33%, 90.00%) than in the control group (26.67%, 50.00%), with statistically significant differences (P<0.05). See **Table 2**.

Comparison of serum sLL-2R, DKK-1 and TSGF levels between the two groups

The differences in sLL-2R, DKK-1 and TSGF levels were insignificant (P>0.05) between the two groups before treatment. However, the level of sLL-2R, DKK-1 and TSGF were decreased in both groups (P<0.05) after treatment, with more significant decreases in the study group in comparison with those in the control group (P<0.05). See **Table 3**; **Figure 1**.

Comparison of miRNA-1290, miRNA-647 and miRNA-182 levels in serum between the two groups

The differences in miRNA-1290, miRNA-647 and miRNA-182 levels were not significant (P>0.05) in serum between the two groups before treatment. While after treatment, miRNA-1290, miRNA-647 and miRNA-182 levels were lower in the study group than in the control group (P<0.05). See **Table 4**.

Comparison of KPS scores between the two groups

Before treatment, the difference was not significant (P>0.05) in KPS scores between the

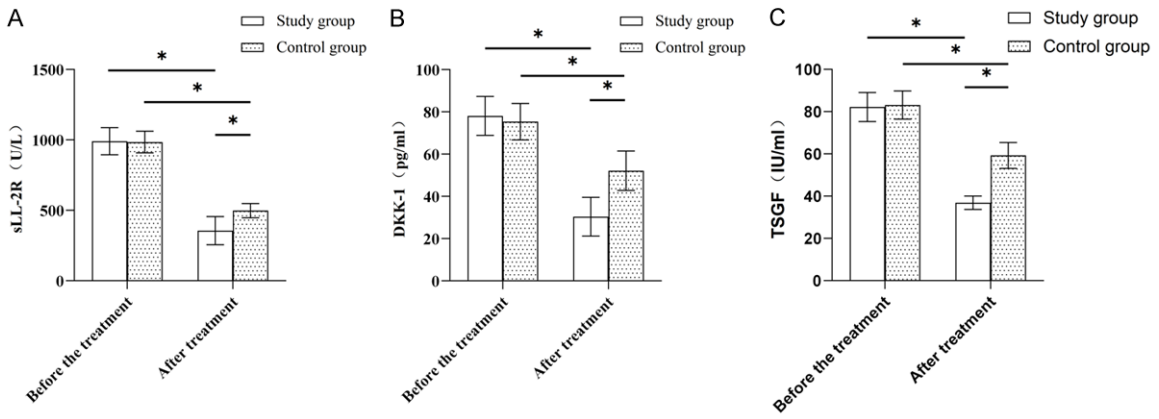

Figure 1. Comparison of serum soluble interleukin-2 receptor (sLL-2R), Dickkopf-1 (DKK-1) and tumor specific growth factors (TSGF) levels between the two groups. A. Comparison of serum SRL-2R levels between the two groups. B. Comparison of serum DKK-1 levels between the two groups. C. Comparison of serum TSGF levels between the two groups. Note: *P<0.05.

Table 4. Comparison of miRNA-1290, miRNA-647 and miRNA-182 levels in serum between the two groups ($\bar{x} \pm s$)

Group	miRNA-1290		miRNA-647		miRNA-182	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n=30)	5.51±0.57	2.06±0.24[a]	4.69±1.50	1.00±0.12[a]	5.22±0.63	3.09±0.48[a]
Control group (n=30)	5.54±0.42	4.09±0.57[a]	4.57±1.08	3.32±0.54[a]	5.20±0.74	5.02±0.53
t-value	0.180	17.880	0.366	22.957	0.113	14.700
P-value	0.858	<0.001	0.716	<0.001	0.910	<0.001

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

Table 5. Comparison of Karnofsky performance status (KPS) scores between the two groups ($\bar{x} \pm s$, points)

Group	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Study group (n=30)	50.50±4.46	67.80±5.94[a]	78.43±6.24[a]	88.63±7.21[a]
Control group (n=30)	49.97±5.11	58.77±5.43[a]	63.50±5.04[a]	76.57±4.82[a]
t-value	0.431	6.145	10.200	7.622
P-value	0.668	<0.001	<0.001	<0.001

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

two groups. KPS scores at 1, 3 and 6 months after treatment were higher in the study group than in the control group (P<0.05). See **Table 5**.

Comparative analysis of the incidence of adverse reactions in the two groups

The differences in adverse reactions, such as vomiting and nausea, diarrhea, decreased white and red blood cells, decreased platelets and abnormal liver function were not significant between the two groups (P>0.05). See **Table 6**.

Comparative analysis of the two groups' survival rates

The study group exhibited higher 1-year, 2-year and 3-year survival rates during follow-up (57.38%, 39.34% and 29.51%) than the control group (32.79%, 18.03% and 8.20%) (P<0.05). See **Table 7**; **Figure 2**.

Discussion

Patients with advanced gastric cancer have often missed the best timing for surgical resec-

Table 6. Comparison of the occurrence of adverse reactions between the two groups [cases (%)]

Group	Nausea and vomiting	Diarrhea	Decreased platelets	Decrease in white blood cells	Decreased red blood cells	Abnormal liver function
Study group (n=30)	5 (16.67)	4 (13.33)	6 (20.00)	8 (26.67)	5 (16.67)	3 (10.00)
Control group (n=30)	4 (13.33)	3 (10.00)	4 (13.33)	6 (20.00)	4 (13.33)	2 (6.67)
χ^2 Value	-	-	0.480	0.373	-	-
P-value	-	-	0.488	0.542	-	-
Fisher's exact probability	1.000	1.000			1.000	1.000

Table 7. Comparative analysis of the two groups' survival rates [cases (%)]

Group	1 year		2 years		3 years	
	Survival	Death	Survival	Death	Survival	Death
Study group (n=30)	25 (83.33)	5 (16.67)	19 (63.33)	11 (36.67)	14 (46.67)	16 (53.33)
Control group (n=30)	17 (56.67)	13 (43.33)	11 (36.67)	19 (63.33)	6 (20.00)	24 (80.00)
Log-rank χ^2 values	4.766		4.777		5.892	
P-value	0.029		0.029		0.015	

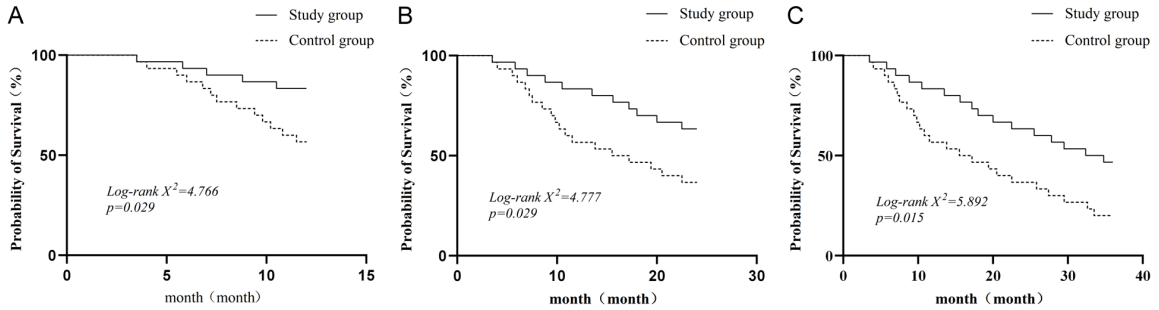

Figure 2. The survival rates of the two groups. A. The 1-year survival rate of the two groups. B. The 2-year survival rate of the two groups. C. The 3-year survival rate of the two groups.

tion. Conventional chemotherapy can effectively kill cancer cells and improve survival rate, but it also damages normal tissue and cells, which is difficult for most patients to tolerate. Camrelizumab is a kind of immune checkpoint inhibitor, humanized immunoglobulin G4 (IgG4) monoclonal antibody. Its mechanism is to block the binding of PD-1 with PD-L1 and programmed death ligand 2 (PD-L2) by targeting PD-1, and finally it promotes the recovery of immune function and plays an anti-tumor effect [14]. Paclitaxel is a classical anti-tumor drug, exerting a significant role in treating lung and ovarian breast cancer as well as many other malignant diseases [15, 16]. Paclitaxel can inhibit the replication of cancer cells and play a role in cancer treatment. With the expansion of the frequency and scope of drug application, it has been found that traditional paclitaxel leads to a high incidence of adverse reactions. Abraxane circumvents the problem of extreme insolubility in water, using albumin as a carrier. Abraxane + paclitaxel can substantially reduce the allergic reaction to paclitaxel and increase the concentration in tumor tissues, contributing to better efficacy in treating malignant tumors and decreased adverse events [17]. Lopressor is the platinum antitumor drug that can stop the replication and transcription of DNA, interfere with the operation of the tumor cell cycle, and play a therapeutic role. Immunotherapy combined with chemotherapy has been applied to various malignant tumors with promising results [18, 19].

In this study, higher disease control rate and overall remission rate were observed in the study group (53.33%, 90.00%) than in the control group (26.67%, 50.00%) with statistically significant differences ($P<0.05$). Higher KPS

scores were observed at 1, 3 and 6 months after treatment in the study group as compared with those in the control group (P<0.05). No significant difference in adverse events was found between the two groups (P>0.05). The results indicate that Camrelizumab combined with Abraxane + lobaplatin is effective in the treatment of advanced gastric cancer by improving the quality of life, probably because immunotherapy combined with chemotherapy can effectively regulate the tumor microenvironment, increase the sensitivity of cytotoxic drugs, thereby playing a synergistic anti-tumor effect [20]. The addition of Camrelizumab in the study group did not increase the incidence of adverse reactions, indicating that Camrelizumab has good safety. According to the study of Zhang et al. [6], the results of this study are consistent with the excellent efficacy and safety of Camrelizumab combined with carboplatin and albumin-bound paclitaxel in treating metastatic or recurrent cervical cancer. sLL-2R is the IL-2R molecule on the cell membrane that is cleaved and shed by the action of enzymes and released into the blood in the form of soluble fragments, which binds to IL-2 and affects its biological activity to exert immunosuppressive effects. Previous studies showed that the level of sLL-2R in malignant tumor tissues was significantly higher than that in normal tissues [21]. DKK-1 belongs to secreted glycoproteins, which has an inhibitory effect on the ENT/β-catenin signaling pathway, and can affect tyrosine phosphorylation and promote the proliferation of tumor cells [22]. TSGF is the general name of polysaccharides and metabolites related to the process of cancer cell proliferation, and it is an endothelial growth factor related to the proliferation of malignant cancer cells and capillaries. TSGF levels in the serum of gastric cancer patients increase as the staging advances [23]. Our results revealed that after treatment, sLL-2R, DKK-1 and TSGF levels were reduced in both groups (P<0.05), with lower levels in the study group than in the control group (P<0.05). It indicates that Camrelizumab combined with Abraxane + lobaplatin for advanced gastric cancer can effectively reduce sLL-2R, DKK-1 and TSGF levels. According to related studies, the combination of immunotherapy and chemotherapy can trigger tumor antigen-specific T lymphocytes to play a synergistic anti-tumor effect [20]. This may be related to chemotherapeutic drugs regulating the tumor immune microenvironment, eliminating immunosuppressive cells in the microenvironment, and playing an immunosuppressive role [24].

The miRNAs are divided into two categories: pro-cancer and anti-cancer. Among them, pro-cancer miRNAs are highly expressed in tumor cells, and their prominent roles are to inhibit apoptosis and promote tumor cell proliferation and metastasis [25-27]. miRNA-1290, miRNA-647 and miRNA-182 showed abnormally high expression in patients with malignant diseases. This study revealed that after treatment, serum miRNA-1290, miRNA-647 and miRNA-182 levels were reduced in both groups (P< 0.05), with comparatively lower levels in the study group (P<0.05). For advanced gastric cancer, it is proposed that the combination of Camrelizumab and Abraxane/lobaplatin can effectively control the levels of the miRNA molecules and improve the therapeutic effect. Comparison of the survival rates of the two groups during follow-up showed that the 1-year, 2-year and 3-year survival rates were higher in the study group (57.38%, 39.34% and 29.51%) than in the control group (32.79%, 18.03% and 8.20%) (*P<0.*05). This indicates that combination treatment can improve the patient's survival. Ren et al. [28] used Camrelizumab combined with paclitaxel/carboplatin to treat advanced non-small cell cancer and found effectively prolonged progression-free survival and overall survival in patients. Luo et al. [29] found that paclitaxel/cisplatin regimen prolonged the survival time of patients with advanced or metastatic esophageal squamous cell carcinoma. It is suggested that Camrelizumab combined with albumin paclitaxel + platinum chemotherapy can effectively improve the survival rate of patients with malignant tumors. The above studies have proven that combining immunotherapy and chemotherapy can play a synergistic anti-tumor effect. The advantage of Camrelizumab combined with albumin paclitaxel/carboplatin, namely, immunotherapy combined with chemotherapy, for advanced gastric cancer can effectively regulate tumor microenvironment, increase cytotoxic drug sensitivity and play a synergistic anti-tumor effect. Additionally, paclitaxel/carboplatin chemotherapy effectively treats locally advanced gastric cancer. Compared with traditional paclitaxel, albumin paclitaxel has the advantages of low toxicity, sound effect, no hor-

mone treatment, and synergistic advantage with immunotherapy.

The study has some limitations, as this study did not set up a Camrelizumab monotherapy group, which limits the explanation of the effect and safety of the drugs. Additionally, the sample size was too small, and thus the study results may be biased, so the sample size should be increased in future investigations.

In conclusion, the combination of Camrelizumab with Abraxane/lobaplatin regimen for advanced gastric cancer can effectively regulate patients' serum tumor markers and immune function and improve patients' survival rate.

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Disclosure of conflict of interest

None.

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