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Study on the therapeutic effect of sintilimab combined with modified DCF regimen on advanced gastric cancer and its impact on Th1/Th2 immune balance

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The aim of this study was to observe the therapeutic effect of sintilimab combined with a modified docetaxel + cisplatin + fluorouracil (DCF) regimen on advanced gastric cancer and its effect on Th1/Th2 immune balance. Ninety-eight cases of advanced gastric cancer patients who visited our hospital from April 2020 to May 2022 were selected and divided into 48 cases each in the conventional group and the research group by random number table method; the DCF regimen was adopted in the conventional group, and sintilimab combined with modified DCF regimen was adopted in the research group, and the therapeutic effects of the patients in the two groups and the changes of Th1/Th2 immune indexes were compared. CEA, CA199, CA242, CD168 AQ3, and IL-4 in the study group were lower than those in the conventional group at the end of three cycles of treatment, and the difference was statistically significant ($P < 0.001$). The levels of IFN-γ and IL-4 in the study group at the end of three cycles of treatment were higher than those in the conventional group ($P < 0.001$). The incidence of adverse reactions during treatment in the study group was lower than that in the conventional group ($P < 0.001$), and the grading of adverse reactions in the study group was milder than that in the conventional group. Sintilimab combined with a modified DCF regimen in the treatment of advanced gastric cancer not only improves the therapeutic effect but also positively affects the Th1/Th2 immune balance, which provides better immune regulation for patients with advanced gastric cancer. *Anti-Cancer Drugs* 35: 780–788 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death worldwide. According to global cancer statistics, there are more than one million new cases of gastric cancer and approximately 780 000 deaths each year. Although certain progress has been made in the early diagnosis and treatment of gastric cancer in recent years [1], the treatment of advanced gastric cancer (AGC) still faces huge challenges [2]. Patients with AGC have a low survival rate and poor prognosis, and existing treatment options such as chemotherapy, targeted therapy, and immunotherapy have limitations to varying degrees. At the same time, due to the atypical or lack of specificity of early gastric cancer symptoms, many patients are already at an advanced stage when diagnosed. In the past, AGC mainly used comprehensive treatment based on chemotherapy, and there was a lack of standardized treatment options. Immunotherapy and targeted therapy combined with neoadjuvant chemotherapy are safe and feasible for laparoscopic radical gastrectomy, and the short-term efficacy is satisfactory [3]. Skeletal muscle mass loss, however, occurs frequently during neoadjuvant chemotherapy for locally AGC and adversely affects survival outcomes, with disease progression and increased risk of death [4,5]. In recent years, research on the molecular mechanisms of gastric cancer has made certain progress, and new therapeutic targets and drugs are constantly being developed. Immunotherapy has shown good efficacy in some patients with gastric cancer, providing new hope for the treatment of AGC.

The docetaxel + cisplatin + fluorouracil (DCF) regimen is one of the commonly used chemotherapy regimens for gastric cancer [6]. It is affected by many adverse reactions, such as poor patient tolerance. The modified DCF regimen is to replace cisplatin

and fluorouracil with oxaliplatin + Tigeol. Compared with traditional DCF, patients have higher levels of 5-fluorouracil in their blood and lower adverse reactions [7,8,9]. Oxaliplatin, Tigeon, and docetaxel, however, may interact with each other in their metabolism and mechanism of action in the body, and these interactions may have certain effects on the immune system. Studies have shown that peripheral CD4(+) T cell subsets have a high predictive value for treatment response and prolonged survival outcomes in patients with AGC [10]. Memory PD-1(+)CD8(+) T cells and PD-1(+) CD8(+)T/PD-1(+)CD4(+) T cell ratio may be effective for screening patients with AGC for immunotherapy benefit [11]. And it has become the standard first-line three-drug chemotherapy regimen [12]. 10.9% of patients with modified DCF still had anemia, however, 7.8% of patients had thrombocytopenia, and 10.9% of patients had neutropenia during treatment [13]. It can be seen that the improved DCF regimen still has a certain degree of hematological toxicity, which will in turn affect T cell subsets and break the Th1/Th2 cell balance. Therefore, it is necessary to further improve the immune balance status of patients using the previous modified DCF regimen.

A meta-analysis found that immunotherapy combined with chemotherapy for HER2-negative AGC can achieve significant benefits in terms of progression-free survival (PFS) and overall survival [14]. Sintilimab is a programmed death protein-1 (PD-1) inhibitor that has been proven to have significant efficacy in a variety of solid tumors, especially in advanced HER2-negative patients. The application is, however, cost-effective [15]. Sintilimab has shown good efficacy in combination with chemotherapy, such as combination with petitabine and oxaliplatin (XELOX regimen) [16]. PD-1 inhibitors exert antitumor effects by blocking the immune evasion mechanism of tumor cells and enhancing the antitumor activity of T cells. Response rates to monotherapy are limited, however, making the development of combination treatment regimens particularly important. DCF regimen (docetaxel, cisplatin, and fluorouracil) is a commonly used chemotherapy regimen that has shown certain efficacy in the treatment of AGC. As treatment progresses, however, patients may develop drug resistance, and the side effects of chemotherapy drugs also limit their long-term use. Encouraging efficacy and manageable safety profile of sintilimab in HER2-negative locally advanced G/GEJ cancer [17]. A multicenter, single-arm phase 2 trial (ChiCTR1900024428) [18] found that sintilimab combined with concurrent chemoradiotherapy has promising efficacy and controllable safety in the perioperative treatment of locally advanced gastric/gastroesophageal junction adenocarcinoma, The 1-year overall survival (OS) rate was 92.6%. There are also studies using the combination of apatinib and sintilimab, which is effective and safe for patients with previously unresectable or metastatic advanced gastric/gastroesophageal junction cancer [19]. It can be seen that sintilimab is mostly combined with chemotherapy drugs and is suitable for patients with AGC. How to select an appropriate chemotherapy regimen, however, requires further research.

Some scholars have used nivolumab combined with DCF regimen to treat AGC with definite efficacy. Larger studies are now needed to confirm these findings [20]. Compared with nivolumab, sintilimab is more suitable for second-line systemic chemotherapy and relapsed and refractory gastric cancer. Accordingly, this study hypothesizes that combination treatment regimens can improve therapeutic efficacy by enhancing immune responses and reducing drug resistance. The purpose of this study was to explore the potential effect of sintilimab combined with modified DCF regimen in the treatment of AGC. At the same time, considering the important role of Th1/Th2 immune balance in the tumor immune microenvironment, this study will also evaluate the impact of combined treatment regimens on Th1/Th2 balance in order to provide new strategies for immunotherapy of AGC.

Information and methods

General information

A total of 96 patients with AGC who visited our hospital from April 2020 to May 2022 were selected. Inclusion criteria: (a) diagnosed with gastric adenocarcinoma by histopathological examination; (b) TNM stage III and IV; (c) aged 18–75 years old; (d) cassette score >60 points, expected survival >3 months. Exclusion criteria: (a) severe organ failure; (b) immune system deficiency or dysfunction; (c) those who are allergic to the drugs required for the study; (d) those with tumors in other locations other than gastric cancer or metastatic gastric cancer; (e) those who are intolerant to chemotherapy; (f) those who refuse or discontinue participation in this study. The patients were divided into a conventional group and a research group with 48 cases each using the random number table method. Forty-six cases were finally included in the conventional group (one case dropped out of the group midway and one case developed drug allergy), and all the research group were included. There was no statistical significance in the gender, age, clinical stage, PD-L1 expression, and differentiation degree between the two groups of patients ($P > 0.05$). See Table 1 for details. All patients signed informed consent forms, and this study was reviewed and approved by the Medical Ethics Committee of our hospital.

Treatment methods

Conventional group

The conventional group was treated with the DCF regimen and the modified DCF regimen, and the observation group was treated with sintilimab on the basis of the control group. Modified DCF regimen: on the first day, docetaxel was administered at 60 mg/m^2, intravenous

Table 1 A comparison of general data in the two groups

Group(*n*)	Sex (cases)		Age (years)	Clinical stage (cases)		PD-L1 expression (cases)		Degree of differentiation (cases)	
	Male	Female		III	IV	Positive	Negative	Low differentiation	Highly differentiated
Conventional (46)	36	10	66.23 ± 6.29	28	18	22	24	16	30
Research (48)	37	11	66.27 ± 6.33	28	20	25	23	15	33
X^2/t	0.019[a]		0.421[b]	0.063[a]		0.170[a]		0.133[a]	
P	0.891		0.674	0.802		0.680		0.716	

[a]X^2 test.
[b]*t*-test.

Table 2 Clinical efficacy evaluation methods

Index	Evaluation content and method
CR	All the original lesions disappeared or narrowed to a short axis <10 mm and maintained for 4 weeks
PR	The total diameter of all target lesions was 30% from baseline and maintained for 4 weeks
SD	The target lesion changes are between partial remission and progression
PD	The total maximum diameter of the target lesion was increased by 20% from baseline
ORR	(CR + PR) number/total 100%
DCR	(CR + PR + SD) Case number/total case number: 100%
PFS	Time from the start of immunocombination chemotherapy treatment to the time of disease progression or death from any cause
OS	From initiation of immunochemotherapy to death from any cause or last follow-up

CR, complete response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

infusion for 1 h; on day 1, oxaliplatin 130 mg/m^2, dissolved in 250 ml of 5% glucose solution, intravenous infusion for 1–5 h; on days 1–14, Tigeol capsule 60 mg/m^2, daily take it once each after breakfast and dinner, rest for 1 week, 21 days is a cycle, and observe the effect after 3 cycles.

Research group

The research group used sintilimab combined with the modified DCF regimen, and carried out sintilimab treatment on the basis of the conventional group: day 1: after the injection of the modified DCF regimen, sintilimab (National Pharmaceutical Approval Word S20180016; specification: 10 ml: 100 mg) injection, dosage is 200 mg, intravenous infusion treatment, every 21 days is one cycle. After a week of rest, the next cycle begins, lasting a total of 3 months.

Observation indicators

Clinical efficacy

The follow-up deadline is May 2023. According to the solid tumor evaluation standards, an efficacy evaluation will be carried out in the 3rd month of treatment, which is divided into complete response (CR), partial response (PR), stable disease. There are four efficacy levels: stable disease and progressive disease (PD). See Table 2 for specific evaluation criteria. And collect the patient's overall effectiveness rate (objective response rate, ORR and disease control rate, DCR). PFS at the end of follow-up is defined as the time from the start of immune combination chemotherapy treatment to disease progression or death from any cause. Survival time (OS) refers to the time from the start of immune combination chemotherapy treatment to death from any cause, time of death or last follow-up.

Serological tests

On the day after the patient is admitted and at the end of three cycles of treatment, 5 ml of morning cubital venous blood is drawn. After letting it stand for 20 min at room temperature, a centrifuge at 3000 r/min is used for centrifugation. The centrifugal radius is set to 15 cm. The supernatant is removed and 3 ml of serum is taken. ELISA kits produced by Siemens (Shanghai, China) were used to detect serum carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 242 (CA242), carbohydrate antigen 168 (CD168) and interferon-γ (IFN-γ), and interleukin 4 (IL-4) levels.

Adverse reactions

The occurrence of diarrhea, abnormal liver and kidney functions, leukopenia, and bone marrow suppression during chemotherapy was recorded in both groups. And the evaluation was graded according to the common terminology criteria for adverse events (CACTE) 5.0.

Survival

Follow-up until May 2023, the survival of patients in both groups was collected, disease progression and death were reassessed, and PFS time and survival time were collected and survival curves were drawn.

Statistical methods

SPSS22.0 (SPSS 22.0 is statistical software developed by IBM) was used for data analysis. The measurement data that passed the normality test and homogeneity of variance test were expressed as (x ± s). Paired *t*-test was performed within the group, and independent sample *t*-test was performed between groups. Count data were expressed as %, rows χ^2 test or Fisher's exact probability. The Kaplan–Meier method was used to draw the survival curve, and the log-rank test was used to compare survival rates. >0.05 indicates statistical difference.

Results

Comparison of clinical outcomes between the two groups

As of May 2023, the median follow-up time of the conventional group was 19.8 months. Forty-six cases were finally included in the conventional group (one case withdrew from the group in the middle and one case developed drug allergy), with an ORR of 47.83% (22/46) and a DCR of 69.57% (32/46); the median follow-up time of the study group was 18.6 months. Finally, 48 patients were included, whose ORR was 75.00% (36/46) and DCR was 87.50% (42/46), and the differences between the groups were statistically significant ($P < 0.05$). See Table 3 and Fig. 1 for details.

Comparison of tumor markers between the two groups

The conventional group and the study group included 46 and 48 patients each, and four tumor markers, CEA, CA199, CA242 and CD168, were tested on the next day of admission and at the end of three cycles of treatment, respectively. The differences between the two groups were not statistically significant before chemotherapy ($t = 1.162$, -0.742, 1.337, 1.379, $P = 0.248$, 0.460, 1.184, 0.171); there was a significant decrease in the levels of CEA, CA199, CA242, and CD168 in the patients of the two groups before and after chemotherapy, and the differences were statistically significant ($P < 0.001$); the study group underwent three cycles of treatment, with a significant decrease in CEA, CA199, CA242, and CD168; CEA, CA199, CA242, and CD168 in the study group were lower than those in the conventional group at the same period after three cycles, and the difference was statistically significant ($t = -13.035$, -13.406, -9.862, -4.911, $P < 0.001$). See Fig. 2 for details.

Comparison of Th1/Th2 cell levels between the two groups

The conventional group and the study group included 46 and 48 patients, respectively, and IFN-γ and IL-4 tests were performed on the next day of admission and at the end of the three cycles of treatment, respectively, and the IFN-γ/IL-4 ratio was calculated. The differences in IFN-γ, IL-4, and IFN-γ/IL-4 between the two groups before chemotherapy were not statistically significant ($t = 1.162$, -0.742, 1.337, 1.379, $P = 0.248$, 0.460, 1.184, and 0.171); the differences in IFN-γ, IL-4, and IFN-γ/IL-4 between the two groups of patients before and after chemotherapy were statistically significant ($P < 0.001$); IFN-γ and IFN-γ/IL-4 were higher in the study group after three cycles than in the conventional group at the same time, and the difference was statistically significant ($t = 16.952$, -11.071, $P < 0.001$); IL-4 was lower in the study group after three cycles than in the conventional group at the same time, and the difference was statistically significant ($t = 18.480$, $P < 0.001$); see Fig. 3 and Table 4.

Comparison of adverse reactions between the two groups

In the conventional group, there were 7 cases of diarrhea, 11 cases of abnormal liver and kidney functions, 7 cases of leukopenia, and 3 cases of bone marrow suppression during the treatment process, of which 12 cases of adverse reactions were graded at grade 3, 9 cases at grade 4, and the rest were graded at grade 1–2; in the research group, there were only 4 cases of diarrhea, 2 cases of abnormal liver and kidney functions, and 1 case of bone marrow suppression during the treatment process; the grading of the adverse reactions was 3 cases at grade 3, 2 cases at grade 4, and the remaining 2 cases were grade 1. The incidence rate of adverse reactions in the research group was lower than that in the conventional group ($\chi^2 = 23.983$, $P < 0.001$); there was no statistical significance in the comparison of the distribution of adverse reaction grades between the two groups ($\chi^2 = 0.413$, $P = 0.521$).

Survival in both groups

Follow-up to May 2023, there were 14 patients with progression in the conventional group, with a PFS of (21.57 ± 13.90) months, intergroup comparison ($t = 0.478$, $P = 0.634$), 11 deaths, and an OS of (25.48 ± 10.51) months; in the study group, there were 12 patients with progression, with a PFS of (22.85 ± 12.22) months, and 1 death, with an OS was (29.42 ± 10.97) months, and OS was compared between groups ($t = 1.776$, $P = 0.079$); as can be seen in Fig. 4, the OS risk of the study group was lower than that of the conventional group ($\chi^2 = 10.248$, $P = 0.001$).

Discussion

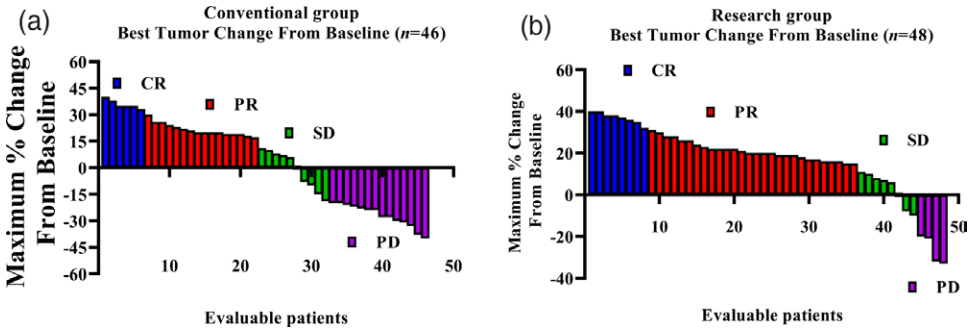
This study aims to explore a new treatment model by combining sintilimab with the traditional DCF regimen in order to achieve better treatment effects. A total of 96 patients with AGC were included and randomly divided

Table 3 Comparison of the clinical efficacy of the two groups (for example)

Group	*n*	CR	PR	SD	PD	ORR (%)	DCR (%)
Conventional (46)	46	6	16	10	14	47.83	69.57
Research (48)	48	8	28	8	4	75.00	87.50
X^2						7.340	4.511
P						0.007	0.034

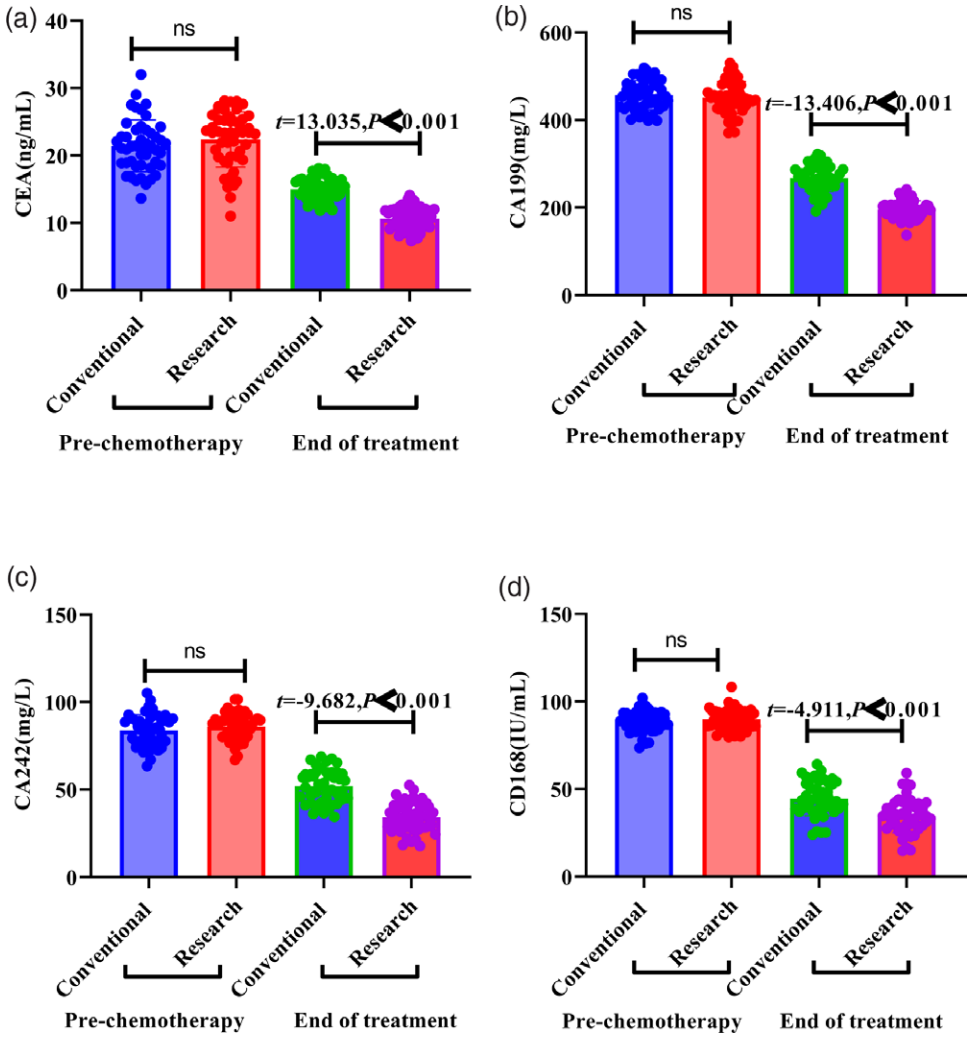
Convention, convention group; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; Research, research group.

Fig. 1



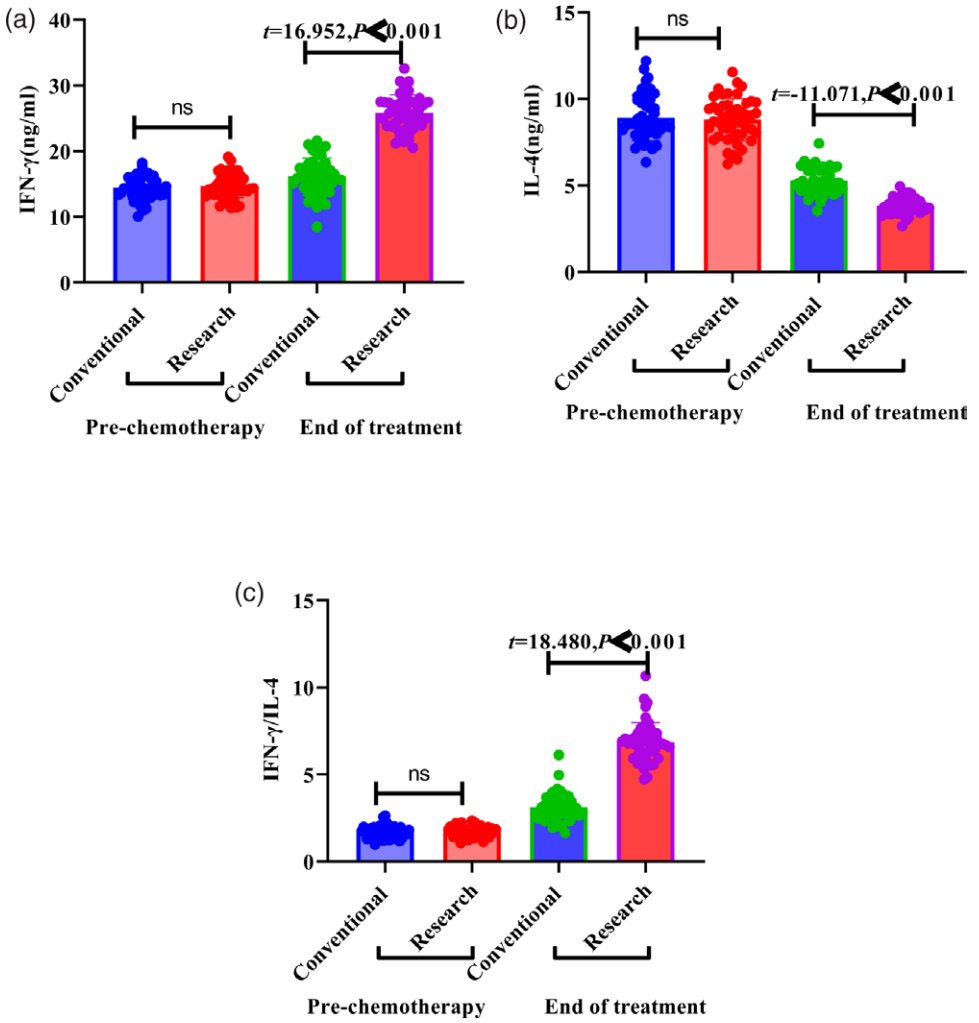
Comparison of the clinical efficacy waterfall charts of the two groups of patients. (a) The clinical efficacy evaluation results of patients in the conventional group and (b) the clinical efficacy evaluation results of the study group.

Fig. 2



Comparison of tumor markers between the two groups. Conventional is patients in conventional group; research is patients in research group; (a) CEA, (b) CA199, (c) CA242, (d) CD168. Prechemotherapy is the next day of admission, end of treatment is three cycles of treatment. ns, $P > 0.05$.

Fig. 3



Comparison of Th1/Th2 cell levels between the two groups of patients. Conventional is conventional group; research is research group; (a) IFN-γ, (b) IL-4, and (c) IFN-γ/IL-4. Prechemotherapy is the next day of admission, and end of teatment is at the time of three cycles of treatment. ns, $P > 0.05$.

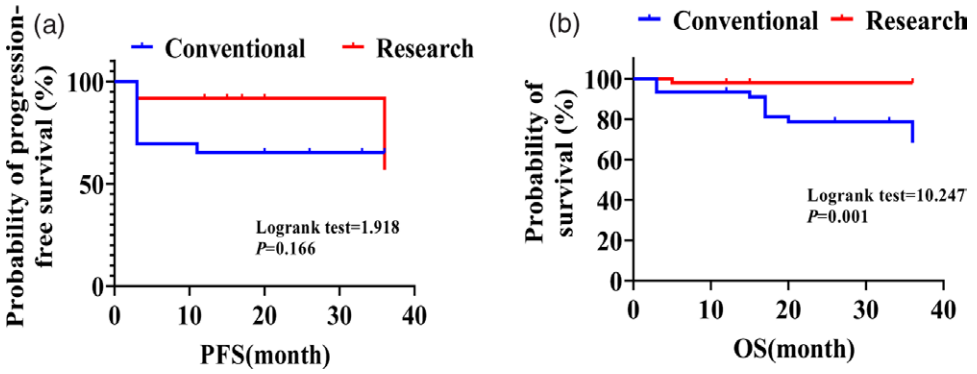
Table 4 Comparison of Th1/Th2 cell levels between the two groups

		IFN-γ(ng/ml)		IL-4 (ng/ml)		IFN-γ/IL-4	
Group	*n*	Prechemotherapy	End of teatment	Prechemotherapy	End of teatment	Prechemotherapy	End of teatment
Conventional	46	14.40 ± 1.80	16.14 ± 2.81*	8.92 ± 1.32	5.29 ± 0.77*	1.65 ± 0.34	3.12 ± 0.80*
Research	48	14.71 ± 1.81	25.83 ± 2.74*	8.81 ± 1.21	3.83 ± 0.47*	1.70 ± 0.29	6.85 ± 1.13*
T		0.828	16.952	−0.417	−11.071	0.721	18.480
P		0.410	<0.001	0.678	<0.001	0.473	<0.001

End of treatment, three cycles of treatment; prechemotherapy, the next day of admission; research, patients in research group; conventional, patients in convention group. Comparison between end of treatment and prechemotherapy in this group, *$P < 0.05$.

into a conventional group and a research group. The conventional group adopted the DCF regimen, while the research group added sintilimab for treatment. Through comparison, it was found that sintilimab combined with the modified DCF regimen can significantly improve the ORR and DCR in patients with AGC, which may be related to the enhancement of the body's Th1 immune response by sintilimab. In recent years, immunotherapy has made breakthrough progress in the field of tumor treatment, especially the application of PD-1/PD-L1 inhibitors, which has provided new treatment options for patients with unresectable AGC [21,22]. Sintilimab, as a PD-1 inhibitor, enhances the body's antitumor immune response by eliminating the immune evasion

Fig. 4



PFS and OS survival curves between the two groups. Conventional is conventional group; research is research group; (a) comparison of progression-free survival analysis and (b) comparison of survival analysis. The higher line represents the better survival of the patients in this group. OS, overall survival; PFS, progression-free survival.

of tumor cells and has played an important role in esophageal cancer, gastric cancer, and other fields [23,24,25]. Patients with AGC often lose the opportunity for radical surgery due to disease progression and metastasis, and the treatment goals mainly focus on relieving symptoms and prolonging survival [26]. IFN-γ and other cytokines produced by Th1 cells can promote cellular immune responses and enhance the killing effect on tumor cells [27]. Based on the fact that IFN-γ belongs to the main signaling pathway in gastric cancer progression [28], PD-1 inhibitors can synergistically increase IFN-γ levels [29]. Traditional chemotherapy regimens, such as DCF (combination therapy of docetaxel, cisplatin and fluorouracil), can alleviate the disease to a certain extent, but their efficacy is limited and accompanied by major side effects. Therefore, it is of great significance to explore new treatment options to improve treatment efficacy and patient tolerance.

The results of this study demonstrate the significant advantages of sintilimab combined with a modified DCF regimen compared with current studies on treatment regimens for AGC in the literature. Although DCF regimen is widely used in the treatment of AGC, its therapeutic effect and patient tolerance still need to be improved. The addition of sintilimab in this study significantly improved the ORR and DCR of treatment. This finding is consistent with the recent positive effects of PD-1 inhibitors in the treatment of various tumors [30]. In addition, by regulating the Th1/Th2 immune balance with sintilimab, the treatment regimen in this study improved the Th1 immune response while inhibiting the Th2 immune response, which may help reduce tumor immune evasion and enhance tumor immune surveillance. The exploration of this mechanism has not been fully reported in previous studies. In terms of tumor markers, this study observed significant decreases in the levels of CEA, CA199, and CA242. CD168 was significantly elevated. Wang *et al.* [31] found that sintilimab combined with neoadjuvant chemotherapy in patients with advanced rectal cancer can suppress CEA levels in patients. Liu *et al.* [32] found that combined use of sintilimab can effectively improve CEA, CA199, and CA125 levels in patients with advanced pancreatic cancer. However, there is still a lack of direct evidence at home and abroad on the impact of sintilimab on CA242 and CD168. In addition, the decrease in IL-4 levels and the increase in IFN-γ levels in the study group further confirmed the positive regulatory effect of the treatment regimen on the immune microenvironment, which has received less attention in previous studies and is one of the innovations of this study. Liang *et al.* [33] believed that compared with chemotherapy alone, sintilimab combined with chemotherapy in the treatment of advanced non-small cell lung cancer can achieve the effect of reducing CYFRA211, CEA, and CA125 and increasing CD3 and CD4 levels. The increased levels of CD3 and CD4 cells will mediate the increase of IFN-γ [34] and inhibit the level of IL-4 [35]. In addition, it is worth noting that although the comparison of PFS between the two groups was not statistically significant, the risk of overall survival in the study group was lower than that in the conventional group, which may indicate the long-term efficacy potential of immunotherapy in AGC. The results in terms of overall survival are similar to the results of studies by many scholars [36,37,38,39]. This has also been reflected in clinical studies of other PD-1 inhibitors, indicating that immunotherapy may provide a new way of long-term survival benefit for patients with AGC. Compared with other studies, however, the sample size of this study is relatively small, and there may be certain selection bias and limitations in the extrapolation of the results. Future studies should be validated in larger patient populations and explore potential biomarkers to predict treatment response, as well as optimization of individualized treatment regimens to further improve treatment efficacy and reduce unnecessary side effects.

In addition, long-term follow-up studies are also necessary to comprehensively evaluate the safety and efficacy of sintilimab combined with modified DCF regimen in the treatment of AGC.

Although this study achieved positive results in exploring the effect of sintilimab combined with a modified DCF regimen in the treatment of AGC and its impact on Th1/Th2 immune balance, there are still some limitations and deficiencies that need to be addressed in future studies and optimization. First, the sample size of this study was relatively small, which may limit the extrapolation and statistical power of the results. In addition, due to the single-center study, patient selection may be biased, which may affect the generalizability of the results. Future studies should be conducted in a multicenter, large-sample setting to enhance the representativeness and reproducibility of the study. Secondly, this study did not involve long-term follow-up data, and there was insufficient information on patient quality of life, long-term survival rate, and potential long-term side effects. Therefore, long-term follow-up studies are necessary to fully evaluate the safety and effectiveness of treatment options. In addition, this study failed to explore the differences in the efficacy of sintilimab combined with the modified DCF regimen on different molecular subtypes of gastric cancer. Future research should consider the molecular heterogeneity of gastric cancer and how to provide patients with personalized treatment based on the molecular characteristics of the tumor treatment options [40]. Finally, although this study observed the positive impact of immunotherapy on Th1/Th2 immune balance, the in-depth mechanism of the immune microenvironment was insufficiently explored. Future research needs to use advanced immunology technology and bioinformatics methods to conduct in-depth studies of immune cell subpopulations, immune checkpoint molecules, and other factors that may affect immune response to reveal the mechanism of action of immunotherapy and provide a basis for predicting treatment response and optimizing treatment plans.

Conclusion

This study, through a prospective, randomized clinical trial design, deeply explored the efficacy of sintilimab combined with the modified DCF regimen in the treatment of AGC and its improvement in Th1/Th2 immune balance. The results of the study show that compared with the traditional DCF regimen, the addition of sintilimab significantly improved the patient's ORR and DCR, while effectively regulating the Th1/Th2 immune balance. This finding provides a new direction for the immunotherapy of AGC. Provides new perspectives and treatment strategies. From the perspective of academic value, this study is not only beneficial to revealing the mechanism of immunotherapy by regulating the Th1/Th2 balance in the tumor microenvironment to enhance antitumor immune responses. This discovery enriches the theoretical basis of gastric cancer immunotherapy and provides important biomarkers for subsequent immunotherapy research. In terms of scientific research level, this study adopted a strict random grouping method and scientific statistical analysis methods to ensure the reliability, rigor, and validity of the academic research results.

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L.C. and L.Q. wrote the main manuscript. Y.C. prepared the data collection. J.Z. prepared figures and tables. S.W. and S.L. analyze and interpret results. All authors reviewed the results and approved the final version of the manuscript. All authors would be informed each step of manuscript processing including submission, revision, revision reminder, etc.

All the authors confirm that all methods were carried out in accordance with relevant guidelines and regulations. Research involving human participants, human material, or human data, must have been performed in accordance with the Declaration of Helsinki.

All the authors confirm that all experimental protocols were approved by a ethics committee of Fengxian District Central Hospital.

All the authors confirming that informed consent was obtained from all subjects and/or their legal guardian(s).

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

There are no conflicts of interest.

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