

## ORIGINAL RESEARCH

# Effect of anlotinib combined with camrelizumab on clinical efficacy and short-term prognosis in male patients with advanced gastric cancer

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**Abstract**

This study aimed to investigate the effects of combining anlotinib with camrelizumab on clinical efficacy and short-term prognosis in male patients with advanced gastric cancer. A total of 88 male patients admitted to our hospital between May 2019 and March 2022 with advanced gastric cancer were included and randomly assigned to Group A (treated with anlotinib alone) or Group B (treated with anlotinib combined with camrelizumab) using the envelope method, with 44 patients in each group. Their clinical efficacy, vascular endothelial growth factor (VEGF) and programmeddeath-1 (PD-1) expression on Cluster of differentiation 4+ (CD4+) and cytotoxic T lymphocyte (CD8+ T) cells in peripheral blood, immune function parameters, tumor markers, incidence of adverse reactions and survival time were compared. The results showed that the patients in Group B had significantly higher objective response rate (ORR) and disease control rate (DCR), superior PD-1 in VEGF, CD4+ T cells and CD8+ T cells, significantly improved immune function indicators and tumor markers (Carbohydrate antigen 50 (CA50), carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA21-1)), and significantly longer progression-free survival and overall survival than Group A. In addition, no significant difference in the incidence of adverse reactions between the two groups was observed. Therefore, the combination of anlotinib and camrelizumab could be a clinically beneficial treatment option and recommended for male patients with advanced gastric cancer as it can effectively control tumor progression, improve clinical efficacy and prolong their survival without increasing adverse reactions.

**Keywords**

Anlotinib; Camrelizumab; Male; Advanced gastric cancer; Clinical efficacy; Short-term prognosis

## 1. Introduction

Gastric cancer is a highly prevalent and deadly malignant tumor that poses a significant threat to human health [1]. It is currently the third most common cancer globally, has a high clinical mortality rate, can take on various forms morphologically, and has an age-related specificity, with the risk of developing the disease increasing after age 40 and peaking at age 75. While some regions have seen a decline in gastric cancer incidence, the disease still accounts for over 1 million new cases and 78,400 deaths worldwide annually. Lower rates of gastric cancer and mortality have been linked to various factors, such as reduced consumption of salted, pickled, smoked, and chemically preserved foods that contain nitrates and increased intake of fresh fruits and vegetables. Gastric cancer is more common in males and may be due to factors such as smoking, occupational stress, eating disorders, or hormonal imbalances. Therefore, it is crucial to take these risk factors into account when considering preventative measures

and treatment options for gastric cancer.

Gastric cancer often presents with subtle symptoms, making it difficult to detect in its early stages. Consequently, a significant number of patients are diagnosed during the middle or advanced stages, leading to a poor clinical prognosis [2, 3]. Previous clinical experience has demonstrated [4, 5] that chemotherapy should remain the primary treatment for advanced gastric cancer, as other therapies have exhibited limited clinical effectiveness. Although surgery is typically an essential component of treatment, offering the best opportunity for long-term survival, it may not be feasible for patients who cannot tolerate it or those with extensively spread cancer, whereby alternative treatments, including chemotherapy and radiation therapy, can be employed instead of surgery.

Patients with poor response to first-line chemotherapy may be considered for second-line chemotherapy, which can show significant differences in clinical efficacy [6]. However, delayed subsequent treatment can limit the effectiveness of other treatment options, emphasizing the need for research on third-

line chemotherapy regimens for advanced gastric cancer [7, 8]. With the continuous advancement of medical technology, multi-target inhibitors have emerged as advantageous in the clinical treatment of advanced cancer, particularly in inhibiting angiogenic antibodies. In line with the therapeutic concept of combining anti-angiogenesis targeted inhibitors with PD-1 inhibitors, our hospital has actively summarized clinical experience and applied a treatment regimen of anlotinib combined with camrelizumab for male patients with advanced gastric cancer. The synergistic effect of the two drugs was shown to effectively reduce the invasion and migration of tumor cells while enhancing their killing effect. Overall, the use of anlotinib integrated with camrelizumab has been found to be effective in controlling tumor progression, improving clinical efficacy and prolonging patient survival without an increase in adverse reactions. Herein, we performed a comparative study on its clinical efficacy in male patients with gastric cancer.

## 2. Materials and methods

### 2.1 Clinical data

A total of 88 male patients with advanced gastric cancer, who were admitted to our hospital between May 2019 and March 2022, were included in this study. The patients were randomly assigned to either Group A or Group B using the envelope method, with 44 patients in each group.

(1) Inclusion criteria: Patients who met the relevant diagnostic criteria for gastric cancer with Tumor Node Metastasis (TNM) stage IIIB–IV; did not respond or had progressed despite receiving a second-line chemotherapy regimen; had normal liver and kidney function; and provided informed consent for study participation (by the patients themselves or their families).

(2) Exclusion criteria: Patients who received surgical treatment, had a life expectancy of less than 3 months, and were allergic to the drugs used in this study.

### 2.2 Treatment methods

#### 2.2.1 Group A

Patients in this group were treated with oral anlotinib hydrochloride capsules (manufactured by Chia Tai Tianqing Pharmaceutical Group Co., Ltd.; State medical permit number: H20180003; Strength: 10 mg based on C<sub>23</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>3</sub>) at a dosage of 10 mg/d for 14 days followed by a 7-day rest period. Each treatment cycle lasted for 21 days, and the treatment was continued for 4 cycles.

#### 2.2.2 Group B

Patients in this group were treated with intravenous injection of camrelizumab for injection (manufactured by Suzhou Sun-cadia Biopharmaceuticals Co., Ltd.; approval number: State medical permit number: S20190027; Strength: 200 mg/bottle) at a dosage of 200 mg per day for 14 days of continuous treatment followed by a 7-day rest period. The treatment cycles and length of treatment were the same as Group A.

### 2.3 Outcome measures

#### (1) Clinical efficacy

Complete response (CR): loss of opacification; partial response (PR): decrease in the diameter of opacification by more than 30%; stable disease (SD): decrease in the diameter of opacification by less than or equal to 30% or increase by less than 20%; and progressive disease (PD): increase in opacification diameter by more than 20%, or the discovery of new lesions.

#### (2) Serum vascular endothelial growth factor (VEGF)

Enzyme-linked immunosorbent assay (ELISA) was used to detect VEGF levels, and the specific procedures were performed according to the relevant kit manual.

#### (3) PD-1 on peripheral blood CD4+ T cells and CD8+ T cells

CD4+, CD8+ and PD-1 monoclonal antibodies were adopted for labeling, respectively, and flow cytometry was applied for relevant operations.

#### (4) Immune function indicators

The levels of CD3+, CD4+ and CD4+/CD8+ in the peripheral blood of patients were measured by flow cytometry.

#### (5) Tumor marker indicators

Carbohydrate antigen 50 (CA50), carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA21-1) were measured by radioimmunoassay and electrochemiluminescence, respectively.

#### (6) Incidence of adverse reactions

(7) Survival time: including progression-free survival and overall survival.

### 2.4 Method of sample size calculation

The sample size was calculated using PASS 15.0 (NCSS, LLC, Kaysville, UT, USA) software, with a test level  $\alpha$  value set at 0.05 and a power  $1-\beta$  value of 0.95. Based on a previous study, the effective rate was 95.00% in the intervention group and 65.00% in the control group. Using these values, a sample size of 40 cases was calculated for each group. However, to account for potential sample loss, the sample size was increased by 10%, resulting in a total of 88 patients recommended for this study.

### 2.5 Statistical methods

Data analysis was performed using SPSS 23.0 (IBM SPSS Inc., Chicago, IL, USA). Enumeration data are presented as  $n$  and %, and comparisons between groups were conducted using the  $\chi^2$  test. Measurement data are presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), and the  $t$ -test was used for comparisons.  $p < 0.05$  was used to indicate statistical significance.

## 3. Results

### 3.1 Comparison of clinical data between two groups

We observed no significant differences in various clinical data, such as height, weight, age, underlying disease, smoking history, family history of gastric cancer, disease location, anemia, tumor diameter, TNM stage, Eastern Cooperative Oncology Group (ECOG) score, microsatellite instability status, and

census register, between Group A and Group B. The detailed results are presented in Table 1.

### 3.2 Comparison of clinical efficacy between two groups

The ORR and DCR in Group B were significantly higher than in Group A ( $p < 0.05$ ). The corresponding results are shown in Table 2.

### 3.3 Comparison of PD-1 in VEGF, CD4+ T cells and CD8+ T cells between both groups

Before treatment, there were no significant differences in PD-1 expression in VEGF, CD4+ T cells and CD8+ T cells between Group A and Group B. However, after treatment, both groups showed significant improvements in the above indicators, with Group B showing significantly greater improvement than Group A ( $p < 0.05$ ). These results are presented in Supplementary Table 1.

### 3.4 Comparison of immune function indicators between two groups

Before treatment, there were no significant differences in CD3+, CD4+ and CD4+/CD8+ levels between Group A and Group B. However, after treatment, Group B showed significant improvement in terms of immune function indicators compared to Group A ( $p < 0.05$ ). These results are presented in Supplementary Table 2.

### 3.5 Comparison of tumor marker indicators between two groups

Before treatment, we observed no significant differences in tumor marker indicators, including CA50, CEA and CYFRA21-1, between Group A and B. However, after treatment, although both groups showed significant improvement in these indicators, Group B demonstrated significantly greater improvement than Group A ( $p < 0.05$ ) (Supplementary Table 3).

### 3.6 Comparison of incidence of adverse reactions between two groups

Comparison in the incidence of adverse reactions, such as decreased appetite, fever, anemia, asthenia, hepatic injury, hypothyroidism and vascular proliferation, showed no significant differences between the two groups (Table 3).

### 3.7 Comparison of survival time between two groups

Herein, we observed that the progression-free survival and overall survival in Group B were significantly longer than in Group A ( $p < 0.05$ ). The corresponding results are shown in Table 4.

## 4. Discussion

Advanced gastric cancer patients who fail to respond to first-line therapy face a high risk of relapse, progression, and ultimately, increased mortality rates [9]. In such cases, person-

alized second-line treatments are administered based on prior clinical practice and patient tolerance. However, the effectiveness of these treatments varies significantly due to differences in individual patient conditions [10], with some patients not experiencing any notable improvements in survival. Currently, there is a lack of clear criteria and clinical study data for third-line treatment options for advanced gastric cancer. Nevertheless, the ongoing advancement of medical technology has led to the development of multi-target inhibitors, particularly anti-angiogenic antibodies [11], which have shown promise in treating advanced cancer and gained increasing attention in clinical practice, demonstrating potential advantages for managing advanced gastric cancer.

Immune escape, a crucial mechanism in the formation and progression of malignant tumors, has become a vital focus in clinical research [12]. Studies have found [13, 14] that PD-1 acts as an innate inhibitor of immune responses, suppressing T cell activity and impairing T cell function, ultimately reducing their effectiveness against tumors. By inhibiting PD-1, T cell activity can be improved, bolstering their ability to combat tumors. This principle underpins the effectiveness of PD-1 inhibitors in treating advanced solid malignancies [15–17].

The indole group of anlotinib has been found to effectively inhibit Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) and Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), thereby preventing the formation of tumor vasculature and lymphatic vasculature and suppressing tumor metastasis [18, 19]. Relevant clinical data [20, 21] has indicated that the objective response rate and disease control rate of patients with advanced lung adenocarcinoma resistant to previous treatment could reach more than 40% and 80%, respectively, when treated with anlotinib. However, in the clinical practice of advanced non-small cell lung cancer, the above two indicators were only about 7% and 67%, respectively.

PD-1 inhibitors are among the most widely studied immune-targeted drugs in clinical research [22, 23]. As of September 2021, China has approved eight such drugs, including nivolumab and camrelizumab. Nivolumab was the first PD-1 inhibitor approved for gastric cancer treatment in China, significantly addressing the limitations of later-line therapies for this disease. However, its high treatment cost restricts its clinical application [24, 25]. Conversely, camrelizumab is a PD-1 inhibitor developed independently in China. Clinical studies have demonstrated its effectiveness in prolonging overall survival for patients with various tumor types compared to conventional chemotherapy. Additionally, camrelizumab exhibits the lowest toxicity among immune-targeted agents when used in second- or third-line treatment regimens [26, 27].

Based on treatment strategies of combining anti-angiogenesis targeted inhibitors with PD-1 inhibitors, this approach is implemented in our hospital for the clinical treatment of male patients with advanced gastric cancer and achieved good clinical results. The results of this study demonstrated that in terms of clinical efficacy, Group B had significantly higher ORR and DCR than Group A. After treatment, the treatment efficacies in Group B were also superior to Group A, particularly in terms of PD-1 from VEGF, CD4+ T cells, CD8+ T cells, immune function

**TABLE 1. Comparison of clinical data between both groups.**

Indicators	Group B (n = 44)	Group A (n = 44)	t/ $\chi^2$ value	p value
Height (cm)	173.34 ± 13.26	173.41 ± 12.95	0.0251	0.9801
Weight (kg)	75.34 ± 4.15	75.41 ± 4.26	0.0781	0.9380
Age (n, %)				
50~60 yr	13 (29.55)	13 (29.55)		
60~70 yr	22 (50.00)	21 (47.73)	0.0759	0.9628
Over 70 yr	9 (20.45)	10 (22.73)		
Underlying disease				
Diabetes	8 (18.18)	11 (25.00)	0.6041	0.4370
Hypertension	10 (22.73)	10 (22.73)	0.0000	1.0000
Smoking history				
Yes	16 (36.36)	17 (38.64)	0.0485	0.8257
No	28 (63.64)	27 (61.36)		
Gastric cancer family				
Yes	13 (29.55)	14 (31.82)	0.0534	0.8172
No	31 (70.45)	30 (68.18)		
Disease location				
Antrum	10 (22.73)	9 (20.45)		
Gastroesophageal junction	21 (47.73)	22 (50.00)	0.0759	0.9628
Gastric body	13 (29.55)	13 (29.55)		
Anemia				
Yes	4 (9.09)	5 (11.36)	0.1238	0.7250
No	40 (90.91)	39 (88.64)		
Tumor diameter (cm)	6.57 ± 0.82	6.59 ± 0.91	0.1083	0.9140
TNM stage (n, %)				
Stage IIIB	33 (75.00)	34 (77.27)	0.0625	0.8025
Stage IV	11 (11.00)	10 (22.73)		
ECOG score (point)	1.52 ± 0.51	1.48 ± 0.55	0.3537	0.7244
Microsatellite instability status (n, %)				
MSI-H	8 (18.18)	7 (15.91)		
MSI-L	5 (11.36)	6 (13.64)	0.1576	0.9242
MSS	31 (70.45)	31 (70.45)		
Census register				
Nonlocal	4 (9.09)	5 (11.36)	0.1238	0.7250
Local	40 (90.91)	39 (88.64)		

TNM: Tumor Node Metastasis; ECOG: Eastern Cooperative Oncology Group; MSI-H: MicroSatellite Instability-High; MSI-L: MicroSatellite Instability-Low; MSS: MicroSatellite stability.

**TABLE 2. Comparison of clinical efficacy between both groups.**

Group	N	CR (n, %)	PR (n, %)	SD (n, %)	PD (n, %)	ORR (n, %)	DCR (n, %)
Group B	44	0 (0.00)	8 (18.18)	27 (61.36)	9 (20.45)	8 (18.18)	35 (79.55)
Group A	44	0 (0.00)	2 (4.55)	23 (52.27)	19 (43.18)	2 (4.55)	25 (56.82)
$\chi^2$ value	—	—	—	—	—	4.0615	5.2381
p value	—	—	—	—	—	0.0439	0.0221

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

**TABLE 3. Comparison of incidence of adverse reactions between two groups.**

Group	N	Decreased appetite	Fever	Anemia	Asthenia	Hepatic injury	Hypothyroidism	Vascular proliferation
Group B	44	9 (20.45)	7 (15.91)	7 (15.91)	6 (13.64)	5 (11.36)	4 (9.09)	2 (4.55)
Group A	44	10 (22.73)	8 (18.18)	7 (15.91)	7 (15.91)	6 (13.64)	4 (9.09)	0 (0.00)
$\chi^2$ value	—	0.07	0.08	0.00	0.09	0.10	0.00	2.05
<i>p</i> value	—	0.80	0.78	1.00	0.76	0.75	1.00	0.15

**TABLE 4. Comparison of survival time between two groups.**

Group	N	Progression-free survival (mon)	Overall survival (mon)
Group B	44	4.72 ± 0.51	11.25 ± 1.06
Group A	44	3.00 ± 0.43	9.00 ± 0.84
$\chi^2$ value	—	17.1031	11.0352
<i>p</i> value	—	0.0000	0.0000

indicators and tumor markers such as CA50, CEA and CYFRA21-1. Progression-free survival and overall survival were also significantly longer in Group B compared to Group A, and the incidence of adverse reactions in Group B, despite using combination therapy, was similar to that of Group A. Thus, the combination of anlotinib and camrelizumab could be used to achieve greater clinical effectiveness for treating advanced gastric cancer in males compared to anlotinib alone, which is consistent with previous reports [28].

In-depth studies discovered [29, 30] that the combination of the two drugs not only exerts the anti-angiogenic effect of tyrosine kinase inhibitors but also has the potential to enhance immune function like PD-1 inhibitors, thereby effectively reducing the invasion and migration ability of tumor tissues and cells while enhancing their killing effect.

## 5. Conclusions

In conclusion, the combination of anlotinib and camrelizumab demonstrated significant benefits in controlling tumor progression, improving clinical efficacy, and prolonging patient survival without increasing adverse reactions in male patients with advanced gastric cancer. Considering that this present study was limited by the predominantly male patient population and relatively small sample size and relatively short post-treatment follow-up time, further studies with larger sample sizes and longer follow-up periods are necessary to validate the clinical effectiveness of this treatment regimen.

### AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper, and any raw data can be obtained from the corresponding author upon request.

### AUTHOR CONTRIBUTIONS

TLX—designed and performed the study; TLX, YSC, YPW, RG, JH and QDD—supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the People's Hospital of Susong County (Approval no. 2019029). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.jomh.org/files/article/1663426736407101440/attachment/Supplementary%20material.docx>.

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