Am J Transl Res 2024;16(8):4032-4041
www.ajtr.org /ISSN:1943-8141/AJTR0157602

Original Article

Efficacy of bevacizumab combined with apatinib in the treatment of advanced metastatic gastric cancer

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Received May 7, 2024; Accepted July 7, 2024; Epub August 15, 2024; Published August 30, 2024

Abstract: Objective: To evaluate the clinical efficacy and safety of bevacizumab combined with apatinib in the treatment of advanced metastatic gastric cancer, providing insights for treatment decisions. Methods: We conducted a single-center retrospective study involving patients with metastatic gastric cancer treated with apatinib, with or without bevacizumab, between August 2018 and April 2021 at Nanchang Medical College. Data on efficacy, adverse events, response rates, and quality of life were collected and compared. Results: No significant differences were observed in complete remission, partial response, stable disease, disease progression, objective response rate, or disease control rate between the groups (all P>0.05). The median progression-free survival was 9.23 months in the control group and 9.94 months in the observation group (P=0.587). Median overall survival (OS) was 19.64 months in the control group and 26.44 months in the observation group (P=0.187). Univariate and multivariate analyses identified combination therapy with apatinib and bevacizumab, primary lesion resection, and number of metastatic organs as independent prognostic factors for OS. Scores for role, emotional, somatic, cognitive, and social functions were significantly higher in the observation group post-intervention (all P<0.05). Conclusions: In patients with advanced metastatic gastric cancer, combined therapy with bevacizumab and apatinib significantly improved OS, enhanced response rates, and increased rates of early and maximal tumor shrinkage.

Keywords: Bevacizumab, apatinib, advanced metastatic gastric cancer, efficacy

Introduction

Gastric cancer, the second most common malignant tumor of the digestive tract, and it accounts for over one million new cases annually worldwide, with approximately 800,000 deaths [1, 2]. In China, it represents 42.5% of global cases, with a mortality rate of 45.0% [3]. Known for its high malignancy, rapid progression, and drug resistance, gastric cancer is often diagnosed at advanced stages due to low early detection rates (2%-4%) [4, 5].

Surgery is the primary treatment, but many patients present with unresectable tumors or metastases, necessitating chemotherapy to improve survival and quality of life [6]. However, traditional therapies have shown limited efficacy in recurrent or metastatic cases.

Angiogenesis, particularly through vascular endothelial growth factor (VEGF), plays a critical role in tumor progression [7, 8]. Apatinib, a tyrosine kinase inhibitor, targets VEGF receptors to inhibit tumor angiogenesis and growth [9-11]. Clinical studies have demonstrated its efficacy and safety in stage IV gastric cancer [12-15]. Common adverse effects include non-hematological toxicities such as hypertension, hand-foot syndrome, and proteinuria [16].

Due to these side effects, there is growing interest in combination therapies, such as apatinib with bevacizumab, to enhance treatment outcomes in advanced gastric cancer.

Bevacizumab, also known as Avastin, is a monoclonal antibody targeting VEGF [17]. It is utilized in treating various cancers such as colorectal, lung, breast, kidney, and glioblastoma multiforme [18-22]. Bevacizumab works by inhibiting angiogenesis, thereby depriving tumors of oxygen and nutrients needed for growth [23]. Common side effects include hypertension,

proteinuria, bleeding, and gastrointestinal perforation [24].

Clinical trials have demonstrated that combining bevacizumab with chemotherapy improves overall survival (OS) and progression-free survival in advanced gastric cancer [25]. Food and Drug Administration approval extends its use to patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have previously undergone chemotherapy.

However, the effectiveness and safety of extending the interval of bevacizumab combined with apatinib for metastatic gastric cancer remain unexplored. This study aims to compare the efficacy and adverse reactions of standard interval bevacizumab-apatinib combinations for metastatic gastric cancer, analyze prognostic factors, conduct subgroup analyses, and evaluate patient quality of life.

Methods

Study design and participants

This single-center retrospective study included patients with metastatic gastric cancer who received apatinib with or without bevacizumab between August 2018 and April 2021 at Nanchang Medical College. The observation group (n=45) received apatinib (Jiangsu Hengrui Medicine Co., Ltd., Art. No.: 20140105) combined with bevacizumab (Shanghai TheraMabs Bio-technology Co., Ltd., Item No.: TM-BAVA-00002-1). The control group (n=55) received apatinib alone (Jiangsu Hengrui Medicine Co., Ltd., Art. No.: 20140105).

Inclusion and exclusion criteria

Inclusion criteria: (1) Histopathological confirmation of gastric adenocarcinoma through gastroscopic or postoperative pathology [26]. (2) Patients treated with apatinib or pembrolizumab, alone or in combination, with available imaging data for disease response assessment and an expected survival time of at least 3 months [26]. (3) Absence of mental disorders or cognitive impairment. (4) Age ≥18 years without significant hearing loss, visual impairment, or dementia before treatment. Exclusion criteria: (1) Prior radiotherapy to the target lesion. (2) History of or concurrent other malignancies. (3) Allergic reactions to apatinib, bevacizumab, or other contraindications affecting drug use. (4) Pregnancy or lactation. (5) History of mental illness or cognitive impairment. (6) Lack of regular monitoring of liver and kidney function post-medication. (7) Incomplete medical records, non-compliance with follow-up, or loss to follow-up.

The study protocol was approved by the Institutional Review Board of Nanchang Medical College. No informed consent was obtained as all data were collected and analyzed anonymously.

Treatment

The control group received apatinib chemotherapy (Jiangsu Hengrui Medicine Co., Ltd., Art. No.: 20140105, 850 mg per dose, orally once daily for 2 weeks). The observation group received combination therapy with apatinib (Jiangsu Hengrui Medicine Co., Ltd., Art. No.: 20140105, 850 mg per dose, orally once daily for 2 weeks) and bevacizumab (Shanghai TheraMabs Bio-technology Co., Ltd., Item No.: TM-BAVA-00002-1, 5 mg/kg intravenously every two weeks).

Definitions and study outcomes

Recent Efficacy: Assessed according to the Response Evaluation Criteria in Solid Tumors [27]:

Complete Response (CR): Disappearance of all target lesions for more than four weeks.

Partial Response (PR): Decrease of 30% or more in the sum of the longest diameters of target lesions from baseline, lasting for more than four weeks.

Stable Disease (SD): Decrease in the sum of the longest diameters of target lesions that does not meet PR criteria, or an increase that does not meet Progressive Disease (PD) criteria.

PD: Increase of 20% or more in the sum of the longest diameters of target lesions, or the appearance of new lesions.

Objective Response Rate (ORR): CR + PR.

Disease Control Rate (DCR): CR + PR + SD.

Table 1. Comparison of general clinical data between the two groups

	Control group (n=55)	Observation group (n=45)	t/χ^2	P
Gender			1.658	0.874
Male	33 (60.00%)	29 (64.44%)		
Female	22 (40.00%)	16 (35.56%)		
Age	57.65±1.47	56.89±1.51	1.001	0.954
Creatinine clearance rate	82.65±2.84	82.17±3.07	1.123	0.927
Primary lesion resection	38 (69.09%)	34 (75.56%)	1.029	0.929
Number of transferred organs			1.778	0.786
1	29 (52.73%)	23 (51.11%)		
>1	26 (47.27%)	22 (48.89%)		
Pathological type			1.739	0.823
Low differentiation	6 (10.91%)	8 (17.78%)		
Middle differentiation	40 (72.73%)	33 (73.33%)		
Highly differentiated	9 (16.36%)	4 (8.89%)		
CEA level			2.199	0.248
<5 mg/ml	11 (20.00%)	14 (31.11%)		
≥5 mg/ml	44 (80.00%)	31 (68.89%)		
ECOG score			2.019	0.657
≤1	43 (78.18%)	39 (86.67%)		
2	12 (21.82%)	6 (13.33%)		
Fundamentals of first-line chemotherapy			0.562	0.074
Ilitacan	32 (58.18%)	18 (40.00%)		
Oxaliplatin	23 (41.82%)	27 (60.00%)		
Cross line use of bevacizumab	35 (63.64%)	23 (51.11%)	2.008	0.267
Number of co used treatment lines			1.778	0.742
Frontline	13 (23.64%)	9 (20.00%)		
Second line	23 (41.82%)	19 (42.22%)		
≥ Three lines	19 (34.54%)	17 (37.78%)		
Number of chemotherapy cycles	13.98±0.87	13.87±1.01	1.837	0.716

Note: CEA: Carcinoembryonic Antigen; ECOG: Eastern Cooperative Oncology Group.

Table 2. Comparison of short-term efficacy between the two groups

Curative effect	Control group (n=55)	Observation group (n=45)	χ^2	P
Complete remission	0 (0.00%)	1 (2.22%)	3.316	0.923
Partial relief	26 (47.27%)	22 (48.89%)	2.695	0.897
Stable	26 (47.27%)	21 (46.67%)	0.022	0.995
Disease progression	3 (5.45%)	2 (4.44%)	0.342	0.984
Objective response rate	26 (47.27%)	23 (51.11%)	0.247	0.784
Disease control rate	53 (96.36%)	41 (91.11%)	2.206	1.000

Table 3. Comparison of median PFS between the two groups

Group	PFS (months)	95% CI		P
		Lower limit	Upper limit	
Control group (n=55)	9.23	7.98	10.27	0.587
Observation group (n=45)	9.94	6.87	12.85	

Note: PFS: Progression-Free Survival.

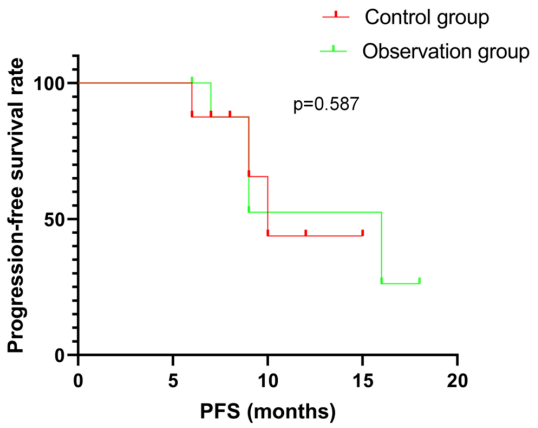

Figure 1. Comparison of median PFS between the two groups. Note: PFS: Progression-Free Survival.

Progression-Free Survival (PFS): Time from treatment initiation to tumor progression or death.

OS: Time from treatment initiation to death.

Adverse Reactions: Bone marrow suppression (manifesting as decreased white blood cells, neutrophils, and platelets), hand-foot syndrome, gastrointestinal reactions, liver and kidney function impairment, hypertension, thrombosis, bleeding, proteinuria, etc.

Secondary outcomes

Quality of Life Assessment: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30) scale was adopted [28]. Lower scores indicate better quality of life.

Comprehensive Patient Data Collection: Gender, age, recurrence and metastasis timelines, creatinine clearance rate, pathological type, Carcinoembryonic Antigen (CEA) levels, primary tumor characteristics (resection status, site), metastatic organ details, local treatment for metastases, chemotherapy cycles and regimens, treatment duration, interval between cycles, treatment-related adverse reactions, progression dates, death dates, and other relevant data sourced from hospital records.

Statistical analysis

Data analysis was conducted using SPSS 25.0 software. For normally distributed continuous data, descriptive statistics included mean and standard deviation. Between-group comparisons were assessed using one-way analysis of variance (ANOVA) with pairwise comparisons performed using the least significant difference (LSD) method. Within-group comparisons utilized paired t-tests. Non-normally distributed continuous data were described using median and quartiles, with inter-group comparisons analyzed using the Kruskal-Wallis H test and pairwise comparisons using the Mann-Whitney U test. Within-group comparisons used the Wilcoxon test. Categorical data were described using frequency and percentage, with inter-group comparisons evaluated using the chi-square test. Ordered logistic regression analysis was employed for multivariate factors. Kaplan-Meier survival curves were plotted, and significance was set at $P<0.05$.

Results

Comparison of general clinical data between the two groups

General clinical data including gender, age, creatinine clearance rate, primary lesion resection, number of metastatic organs, pathological type, CEA level, ECOG score, first-line chemotherapy details, number of treatment lines, and chemotherapy cycles showed no significant differences between the two groups (all $P>0.05$) (**Table 1**).

Comparison of short-term efficacy between the two groups

Table 2 presents the short-term efficacy results between groups. There were no significant differences in complete remission, partial response, stable disease, disease progression, objective response rate, or disease control rate between the two groups (all $P>0.05$).

Comparison of long-term therapeutic effects between the two groups

We compared the long-term therapeutic effects between the two groups. The median PFS was 9.23 months in the control group and 9.94 months in the observation group, with no significant difference ($P=0.587$) (**Table 3** and **Figure 1**). Similarly, the median OS was 19.64 months in the control group and 26.44 months in the observation group, also without signifi-

Table 4. Comparison of median OS between the two groups

Group	OS (months)	95% CI		P
		Lower limit	Upper limit	
Control group (n=55)	19.64	15.41	24.24	0.187
Observation group (n=45)	26.44	17.36	32.37	

Note: OS: Overall Survival.

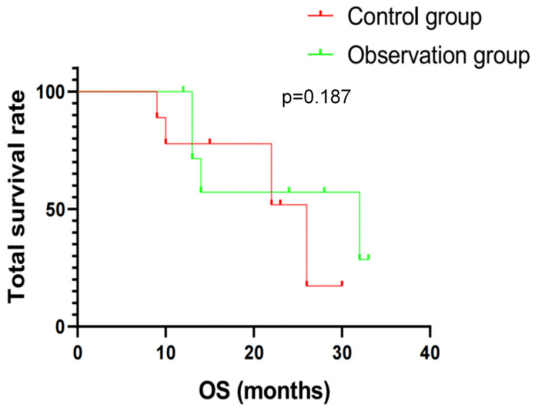

Figure 2. Comparison of median OS between the two groups. Note: OS: Overall Survival.

cant difference (P=0.187) (**Table 4** and **Figure 2**).

Comparison of adverse events between two groups

Adverse events such as leukopenia, neutropenia, thrombocytopenia, liver and renal impairment, hand-foot syndrome, gastrointestinal reactions, hypertension, hemorrhage, thrombosis, and albuminuria showed no significant differences between the two groups (all P>0.05) (**Table 5**).

Univariate and multivariate analysis

Univariate and multivariate analyses indicated that factors such as age (95% CI 0.575-5.954; P=0.43), gender (95% CI 0.719-1.261; P=0.733), primary lesion resection (95% CI 0.080-1.473; P=0.150), number of metastatic organs (95% CI 0.656-1.595; P=0.150), CEA levels (95% CI 0.999-1.009; P=0.111), ECOG score (95% CI 0.990-1.025; P=0.428), first-line chemotherapy details (95% CI 0.091-1.553; P=0.160), and bevacizumab use (95% CI 0.991-1.035; P=0.438) did not significantly impact PFS (**Tables 6** and **7**). However, patient grouping (95% CI 1.398-2.874; P=0.021), primary lesion resection (95% CI 1.068-3.345; P=0.027), and number of metastatic organs (95% CI 1.189-3.487; P=0.014) were independent prognostic factors affecting OS (**Table 8**).

Comparison of the QLQ-C30 scores between the two groups

Analysis of QLQ-C30 scores indicated that compared to the control group, the observation group showed significantly higher scores in role function, emotional function, somatic function, cognitive function, and social function after intervention (all P<0.05) (**Figure 3**).

Discussion

In our study, we observed that combining bevacizumab and apatinib significantly enhances the response rate and promotes early and maximum tumor shrinkage in patients with metastatic gastric cancer. Bevacizumab, a monoclonal antibody targeting VEGF, crucially inhibits angiogenesis - the process of forming blood vessels that supply nutrients to tumors. By blocking VEGF, bevacizumab reduces tumor blood supply, thereby shrinking tumors and inhibiting metastasis [29].

Apatinib, a small molecule tyrosine kinase inhibitor, targets VEGF receptor 2, further disrupting the VEGF signaling pathway and enhancing anti-angiogenic effects [30]. When combined, bevacizumab and apatinib synergistically inhibit tumor growth and metastasis by targeting different components of the VEGF pathway, amplifying their anti-tumor effects beyond what either drug achieves alone [31].

For patients with metastatic gastric cancer who may develop resistance to traditional chemotherapy or targeted therapies, the bevacizumab and apatinib combination offers a promising treatment option. These drugs' distinct mechanisms of action enable them to overcome resistance encountered with other therapies [32]. Clinical studies consistently demonstrate that

Table 5. Comparison of adverse events between the two groups

Project	All levels		P	Level 3-4		P
	Control group (n=55)	Observation group (n=45)		Control group (n=55)	Observation group (n=45)	
Leukopenia	40 (72.73%)	36 (80.00%)	0.978	9 (16.36%)	7 (15.56%)	0.872
Neutropenia	42 (76.36%)	37 (82.22%)	0.904	11 (20.00%)	8 (17.78%)	0.713
Thrombopenia	20 (36.36%)	18 (40.00%)	0.974	7 (12.73%)	5 (11.11%)	0.852
Liver lesion	21 (38.18%)	12 (26.67%)	0.117	4 (7.27%)	2 (4.44%)	0.617
Renal impairment	9 (16.36%)	6 (13.33%)	0.654	3 (5.45%)	0 (0.00%)	1.006
Hand-foot syndrome	41 (74.55%)	34 (75.56%)	0.687	10 (18.18%)	3 (6.67%)	0.154
Gastrointestinal Reaction	39 (70.91%)	35 (77.78%)	0.745	7 (12.73%)	2 (4.44%)	0.207
Hypertension	6 (10.91%)	5 (11.11%)	1.001	0 (0.00%)	0 (0.00%)	-
Hemorrhage	8 (14.55%)	4 (8.89%)	0.374	0 (0.00%)	0 (0.00%)	-
Thrombus	4 (7.27%)	3 (6.67%)	1.001	0 (0.00%)	0 (0.00%)	-
Albuminuria	4 (7.27%)	4 (8.89%)	0.718	0 (0.00%)	0 (0.00%)	-

Table 6. Univariate analysis of influencing factors of PFS

Index	β	SE	OR (95% CI)	Wald	P
Gender	-0.049	0.143	0.952 (0.719-1.261)	0.116	0.733
Age	-0.078	0.099	0.925 (0.761-1.123)	0.623	0.430
Primary resection	-1.069	0.743	0.343 (0.080-1.473)	2.070	0.150
Number of transferred organs	-1.069	0.743	0.343 (0.656-1.595)	2.070	0.150
CEA level	0.004	0.002	1.004 (0.999-1.009)	2.534	0.111
ECOG rating	0.007	0.009	1.007 (0.990-1.025)	0.628	0.428
Basis of first-line chemotherapy	0.226	0.096	1.254 (1.039-1.513)	5.580	0.018
Bevacizumab crossed the line	0.704	0.223	2.023 (1.306-3.132)	9.970	0.002

Note: CEA: Carcinoembryonic Antigen; ECOG: Eastern Cooperative Oncology Group; PFS: Progression-Free Survival.

Table 7. Multivariate analysis of influencing factors of PFS

Index	β	SE	OR (95% CI)	Wald	P
Basis of first-line chemotherapy	-1.079	0.723	0.353 (0.091-1.553)	2.071	0.160
Bevacizumab crossed the line	0.008	0.011	1.037 (0.991-1.035)	0.638	0.438

Note: β: regression coefficient; SE: standard error; OR: odds ratio; PFS: Progression-Free Survival.

this combination therapy significantly improves response rates, enhances tumor control, and prolongs survival in patients with metastatic gastric cancer [33-35].

Our study specifically shows that combining bevacizumab and apatinib markedly improves the survival prognosis of patients with metastatic gastric cancer. Numerous clinical trials have validated the efficacy of this combination in improving OS, progression-free survival, and response rates compared to conventional treatments [36-39]. Incorporating bevacizumab alongside apatinib has proven particularly effective in extending survival durations compared to apatinib alone or other standard therapies [40].

Combining bevacizumab with apatinib has been observed to reduce chemotherapy resistance in patients with metastatic gastric cancer. Bevacizumab exerts immunomodulatory effects by limiting the recruitment of immunosuppressive cells to the tumor microenvironment. This action is achieved through VEGF inhibition, which prevents the formation of new blood vessels crucial for the growth of immunosuppressive cells [41].

Table 8. Univariate and multivariate analysis of influencing factory of OS

Factor	Cases	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Group		0.678 (0.405-0.587)	0.046	2.984 (1.398-2.874)	0.021
Control group	55				
Observation group	45				
Gender		0.806 (0.467-1.387)	0.467		
Male	62				
Female	38				
Age		1.223 (0.707-2.442)	0.448		
<60 years	56				
≥60 years	44				
Primary resection	72	2.125 (1.197-3.058)	0.017	1.879 (1.068-3.345)	0.027
Number of transferred organs		2.187 (1.274-3.871)	0.006	2.034 (1.189-3.487)	0.014
1	52				
>1	48				
CEA level		1.716 (0.874-3.481)	0.135		
<5 mg/ml	25				
≥5 mg/ml	75				
ECOG rating		0.871 (0.687-1.875)	0.687		
≤1	72				
2	18				
Basis of first-line chemotherapy		0.806 (0.477-1.378)	0.417		
Irinotecan	50				
Oxaliplatin	50				
Bevacizumab crossed the line	58	1.287 (0.752-2.107)	0.436		

Note: CEA: Carcinoembryonic Antigen; ECOG: Eastern Cooperative Oncology Group; OS: Overall Survival.

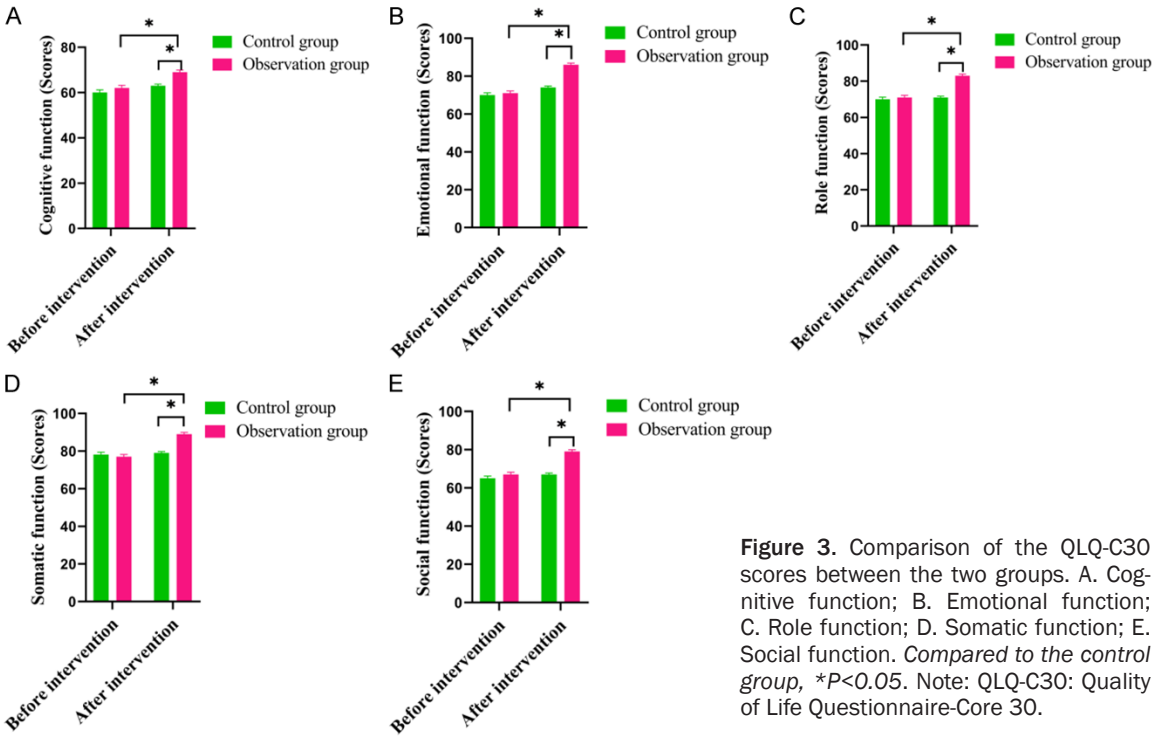

Figure 3. Comparison of the QLQ-C30 scores between the two groups. A. Cognitive function; B. Emotional function; C. Role function; D. Somatic function; E. Social function. *Compared to the control group, *P<0.05*. Note: QLQ-C30: Quality of Life Questionnaire-Core 30.

Apatinib enhances the anti-tumor immune response by suppressing regulatory T cells and myeloid-derived suppressor cells. When used together, these drugs synergistically bolster the anti-tumor immune response, thereby enhancing chemotherapy outcomes [42]. Additionally, bevacizumab and apatinib modulate the tumor microenvironment by reducing hypoxia and acidity, conditions that promote tumor growth and chemotherapy resistance [43]. By normalizing tumor vasculature and improving oxygen levels, these drugs facilitate better delivery of chemotherapy agents to the tumor site, thereby enhancing treatment efficacy [44].

However, our study has several limitations that warrant consideration. Firstly, it included only Chinese patients, limiting the generalizability of findings to other regions. Secondly, the lack of long-term follow-up data hinders assessment of treatment durability. Cancer therapies require continuous monitoring to evaluate long-term benefits and risks associated with treatment. Thirdly, being a single-center retrospective analysis, our study may be susceptible to selection bias. Future research with robust study designs and comprehensive data collection is essential to validate these findings and inform clinical practice.

In summary, combination treatment with bevacizumab and apatinib significantly improves OS, enhances response rates, and promotes early and maximum tumor shrinkage in patients with metastatic gastric cancer.

Disclosure of conflict of interest

None.

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