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ORIGINAL RESEARCH

Comparative Retrospective Analysis of Immunotherapy Combined with Anti-Angiogenic Agents and Nab-Paclitaxel in Metastatic Gastroesophageal Junction Adenocarcinoma

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Objective: Recent years have seen breakthrough progress in the use of immune checkpoint inhibitors in cancer therapy, offering new hope for patients with advanced gastric cancer. However, there remains insufficient real-world evidence regarding the efficacy and safety of combining immune checkpoint inhibitors with anti-angiogenic drugs and chemotherapy in the second-line setting. There is a pressing clinical need for dedicated studies to validate its application value. The present investigation systematically evaluated the clinical efficacy and safety profile of a multimodal therapeutic strategy integrating second-line immunotherapeutic agents, cytotoxic chemotherapy, and anti-angiogenic therapy in patients with metastatic gastroesophageal junction adenocarcinoma.

Methods: A retrospective analysis was conducted on 84 patients treated in the oncology department. Patients were divided into two groups: the observation group (sintilimab + apatinib + albumin-bound paclitaxel, n = 42) and the control group (apatinib + albumin-bound paclitaxel, n = 42). Outcomes included median overall survival (mOS), median progression-free survival (mPFS), objective response rate (ORR), disease control rate (DCR), and adverse event incidence.

Results: Baseline characteristics (age, gender, Eastern Cooperative Oncology Group score, tumor location, histology, Lauren classification, human epidermal growth factor receptor 2 status, programmed death-ligand 1 expression, metastatic status, and prior treatment) showed no significant differences ($P > 0.05$), ensuring comparability. After follow-up, there was no significant difference in ORR or DCR between the two groups ($P > 0.05$): the observation group exhibited an ORR of 42.85% and DCR of 85.71%, compared to 38.09% and 75.57% in the control group, respectively. Furthermore, there was no significant difference in the overall incidence of adverse events or immune-related adverse events between the groups ($P > 0.05$). The incidence of immune-related adverse events was 21.43% (observation group) vs. 23.81% (control group), with no statistical significance ($P = 0.798$). The observation group had significantly longer mPFS (12.0 months vs. 9.0 months, hazard ratio (HR) = 0.455, 95% confidence interval [CI]: 0.217–0.956; $P = 0.028$), though mOS showed no difference (HR = 0.384, 95% CI: 0.131–1.125; $P = 0.062$). Kaplan-Meier analysis confirmed superior PFS in the observation group.

Conclusion: The combination of an anti-PD-1 monoclonal antibody with chemotherapy and anti-angiogenic agents demonstrated preliminary efficacy and favorable safety in second-line gastric cancer patients. This study, using real-world data, validates the clinical benefit of this triple regimen, addresses the evidence gap in second-line treatment options, provides new insights for personalized combination strategies in advanced gastric cancer, and holds significant value for guiding clinical practice.

Keywords: gastric cancer, second-line, immunotherapy, anti-angiogenic agents, albumin-bound paclitaxel

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Introduction

Gastric cancer, with its high incidence and mortality rates globally, poses a serious threat to human life and health. Epidemiological studies indicate that it ranks as the fifth most common malignancy and the fourth leading cause of cancer-related deaths worldwide.[1] In China, the disease burden is particularly severe, imposing substantial societal and familial burdens.[2] Due to its non-specific early symptoms, most patients are diagnosed at advanced stages, missing the optimal window for surgical intervention.[3] For these patients, systemic therapy remains the cornerstone of prolonging survival and improving quality of life.

Over the past decades, chemotherapy has served as the mainstay treatment for advanced gastric cancer.[4] Platinum-based, fluorouracil-based, and taxane-containing regimens have modestly improved survival outcomes, yet their overall efficacy remains suboptimal.[5] The development of drug resistance, coupled with chemotherapy-induced toxicity to normal tissues—including myelosuppression, gastrointestinal disturbances, alopecia, and other adverse effects—significantly compromises patients' quality of life and limits treatment continuity.[6] Thus, while chemotherapy has long been the first-line treatment for advanced gastric cancer and can prolong survival, its efficacy and safety are limited by issues such as drug resistance and adverse reactions including myelosuppression and gastrointestinal toxicity.

Recent breakthroughs in tumor immunology have positioned immunotherapy as a transformative therapeutic modality for advanced gastric cancer. Based on the ATTRACTION-2[7] and CheckMate 649 trials,[8] the programmed death-1 (PD-1) inhibitor nivolumab has been approved for treating advanced gastric cancer. Sintilimab, an anti-PD-1 monoclonal antibody independently developed in China, provides a domestic innovative immunotherapy option for patients with advanced gastric cancer, offering a balance of efficacy, safety, and accessibility. These immune checkpoint inhibitors, which block the immune evasion pathways of tumor cells and reactivate the body's anti-tumor immune response, have become a major research focus in oncology.[9–11] In gastric cancer, ICIs have shown clinical benefit, particularly in programmed death-ligand 1 (PD-L1)-positive patients. However, while some patients achieve durable responses, many exhibit primary or acquired resistance.[12] To overcome resistance, combination strategies with chemotherapy, radiotherapy, and targeted therapies are being explored.[13] Chemotherapy not only directly kills tumor cells but also exerts immunomodulatory effects. Certain chemotherapeutic agents induce immunogenic cell death (ICD), releasing tumor-associated antigens and danger signals to activate antitumor immune responses.[14,15] Chemotherapy additionally modulates the tumor microenvironment through depletion of immunosuppressive cells and activation of immune effector populations, thereby synergizing with immunotherapy.[16] These mechanisms support the rationale for combining chemotherapy with immunotherapy to achieve synergistic effects.[17] Anti-angiogenic therapy also plays a key role in gastric cancer treatment.[18] Tumor angiogenesis supplies oxygen and nutrients while facilitating metastasis.[19] Anti-angiogenic agents targeting vascular endothelial growth factor and its receptors inhibit tumor growth and expansion.[20] However, drug resistance and limited clinical benefits necessitate novel strategies, such as combining anti-angiogenic therapy with chemotherapy or immunotherapy.[21]

The triple combination of immune checkpoint inhibitors, anti-angiogenic agents, and chemotherapy is theorized to exert anti-tumor effects through the synergistic mechanisms of immune activation, vascular inhibition, and cytotoxic killing. Although preliminary evidence from scattered Phase II clinical trials and small-sample real-world data suggests the potential for enhanced efficacy and manageable safety of this regimen in the second-line treatment of advanced gastric cancer,[22,23] systematic studies on this combination remain relatively scarce, and results across studies are inconsistent. Notably, research based on retrospective data collection, while not prospectively designed, holds significant exploratory value in current clinical practice. Such studies can provide preliminary evidence on efficacy and safety for subsequent prospective research and help identify potential beneficiary populations. Although the regimen in this study was not primarily designed by the authors but was analyzed retrospectively based on existing clinical practice and theoretical foundations, this study aims to fill a gap in the current evidence by systematically comparing the differences between the immunotherapy combination group and the chemotherapy plus anti-angiogenic therapy group in terms of objective response rate (ORR), disease control rate (DCR), median overall survival (mOS), median progression-free survival (mPFS), and incidence of adverse events.

Based on this background, this study focuses on the efficacy and safety of second-line application of immune checkpoint inhibitors combined with chemotherapy and anti-angiogenic agents in treating advanced gastric or gastro-esophageal junction adenocarcinoma. By retrospectively analyzing the case data of patients with advanced gastric cancer admitted to the oncology department of our hospital and comparing the efficacy and safety differences between the triple regimen and the anti-angiogenic agent plus chemotherapy regimen, this study aims to provide reliable real-world evidence for second-line treatment of advanced gastric cancer, optimize clinical decision-making, and offer new strategic options for improving patient prognosis.

Materials and Methods

Study Subjects

This single-center retrospective cohort study utilized data from electronic medical records, pathological examination reports, imaging evaluation data, and outpatient/telephone follow-up records of patients with advanced gastric or gastroesophageal junction adenocarcinoma admitted to the oncology department of our hospital from January 2021 to January 2024. All clinical data were independently extracted and cross-verified by two attending oncologists to ensure accuracy and completeness. A total of 84 patients who received second-line therapy with immune checkpoint inhibitors combined with chemotherapy and anti-angiogenic agents during the aforementioned period were retrospectively analyzed as the study subjects. Inclusion criteria: (1) Patients with histologically or cytologically confirmed adenocarcinoma or signet-ring cell carcinoma; (2) Patients with disease progression or intolerance to standard first-line therapy; (3) Patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2; (4) Patients with measurable lesions; (5) Patients receiving sintilimab in second-line therapy; (6) Patients who received at least 2–3 cycles of second-line antitumor therapy and underwent at least one efficacy evaluation; (7) Patients with complete clinical data. Exclusion criteria: (1) Patients with squamous cell carcinoma of the gastroesophageal junction; (2) Patients who underwent surgical treatment; (3) Patients previously treated with anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-CTLA-4 antibodies, or other T-cell inhibitory therapies; (4) Patients who received chemotherapy, molecular targeted therapy, immunotherapy, or radiotherapy within 14 days prior to enrollment; (5) Patients with cachexia, severe hepatic/renal dysfunction, or multi-organ failure; (6) Patients with significant hemorrhagic disorders, vasculitis, or active gastrointestinal bleeding; (7) Patients with arterial thromboembolic events; (8) Patients with inflammatory bowel disease, acute/subacute intestinal obstruction, or chronic diarrhea; (9) Patients with uncontrolled hypertension. The 42 patients receiving sintilimab combination therapy were assigned to the observation group. Retrospective 1:1 matching was performed using SPSS-generated random numbers combined with the visual binning method to select 42 patients with comparable baseline characteristics (such as age and gender) from those receiving dual-drug therapy during the same period as the control group. The matching process was blinded to the personnel responsible for data screening and registration to minimize bias. The study protocol was approved by Affiliated Hospital of Hebei University (No. 212, Yuhua East Road, Baoding City, Hebei Province, China), and all participants provided written informed consent before enrollment. Primary endpoint assessments were performed by two blinded pathologists, and all statistical analyses were conducted by blinded investigators.

Treatment Protocols

In light of the potential for increased toxicity associated with combination therapy compared to monotherapy, and considering the significant immunomodulatory role of chemotherapy within combination regimens, the dosage of chemotherapeutic agents in this study was reduced relative to conventional levels. Participants in the control group were administered albumin-bound paclitaxel at a dose of 150 mg/m^2 via intravenous infusion on the first day of each cycle, prior to chemotherapy, with a frequency of once every three weeks, in conjunction with apatinib at a dose of 250 mg, taken orally within 30 minutes post-breakfast, once daily. Conversely, participants in the observation group received sintilimab at a dose of 200 mg via intravenous infusion within 60 minutes prior to chemotherapy on the first day of each cycle, also every three weeks, in combination with albumin-bound paclitaxel (150 mg/m^2 administered via intravenous infusion on day 1 of each cycle, prior to chemotherapy, once every three weeks) and apatinib (250 mg

administered orally within 30 minutes after breakfast, once daily).Both groups underwent treatment in 4-week cycles, with a minimum of six cycles administered, continuing until either disease progression or the development of unacceptable toxicity. Throughout the treatment course, patients in both groups received comprehensive supportive care. This included intravenous hydration with sodium bicarbonate, oral antiemetic agents such as ondansetron or metoclopramide for the prevention of nausea and vomiting, and subcutaneous injections of recombinant human granulocyte colony-stimulating factor to manage leukopenia. Additionally, blood transfusion support, including packed red blood cells and platelets, was provided as clinically indicated. Prompt anti-infective therapy was initiated in cases of concurrent infections to minimize complications and ensure treatment continuity.

Evaluation and Endpoints

Treatment efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[24] Complete response (CR) was defined as the disappearance of all target lesions and a reduction in the short axis of all pathological lymph nodes to <10 mm. Partial response (PR) was defined as a ≥30% decrease in the sum of the diameters of target lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Progressive disease (PD) was defined as a ≥20% increase in the sum of diameters of target lesions or the appearance of new lesions. The ORR was calculated as (CR + PR), and the DCR was calculated as (CR + PR + SD). Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, documenting the occurrence and time of onset for both drug-related and immune-related adverse events. Progression-free survival (PFS) was defined as the time from enrollment to disease progression or death from any cause. Overall survival (OS) was defined as the time from enrollment to death from any cause. For patients whose death or disease progression could not be confirmed, or who were still alive at the time of analysis, the last follow-up date was used as the censoring date in the survival analysis. The final patient outcomes were obtained through the hospital's electronic medical record system, outpatient system, or telephone follow-up.

Data Analysis

Kaplan-Meier method was employed to generate PFS and OS curves, and statistical analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as number (%), and continuous variables were categorized based on cutoff points. Comparisons of ORR and DCR between groups were conducted using the chi-square test or Fisher's exact test. Kaplan-Meier survival analysis was used to estimate OS and PFS, and differences were assessed using the Log rank test. A significance level of $\alpha = 0.05$ was applied.

Results

Analysis of Baseline Characteristics Between Groups

Comparative analysis of baseline characteristics between the investigational cohort (sintilimab+apatinib -nab-paclitaxel regimen, n = 42) and control cohort (sintilimab-nab-paclitaxel, n = 42) revealed balanced demographic and clinical profiles. No statistically significant differences were observed between the two groups in baseline characteristics, including age, sex, ECOG performance status, tumor location, histology, Lauren classification, HER2 status, PD-L1 expression, metastatic features, and prior treatment history (all $P > 0.05$). This balance in baseline data established a high degree of comparability between the groups, thereby providing a solid foundation for subsequent analyses of efficacy and safety (Table 1).

Correlation Analysis Between Treatment Protocol and Efficacy Outcomes

At the conclusion of the follow-up period, treatment outcomes were assessed for both groups. In the observation group, which received a combination regimen of sintilimab,apatinib, and albumin-bound paclitaxel, CR was observed in 2 patients (4.76%), PR in 16 patients (38.10%), SD in 18 patients (42.86%), and PD in 6 patients (14.28%). In comparison, the control group—treated with sintilimab and albumin-bound paclitaxel alone—had 1 patient (2.38%) achieving CR, 15 patients (35.71%) with PR, 17 patients (40.48%) maintaining SD, and 9 patients (21.43%) showing PD. The ORR was

Table 1 Baseline Clinical Characteristics of the Patients

Patient Data	Observation Group (n=42)	Control Group (n=42)	*P*-value
Age			0.603
< 65 years	34 (80.95%)	31 (73.81%)	
≥ 65 years	8 (19.05%)	11 (26.19%)	
Gender			0.641
Male	27 (64.29%)	30 (71.43%)	
Female	15 (35.71%)	12 (28.57%)	
ECOG Score			0.827
0-1	18 (42.86%)	20 (47.62%)	
2	24 (57.14%)	22 (52.38%)	
Tumor Location			0.588
Gastroesophageal junction	7 (16.67%)	10 (23.81%)	
Gastric cancer	35 (83.33%)	32 (76.19%)	
Histological Type			0.615
Adenocarcinoma	33 (78.57%)	30 (71.43%)	
Adenocarcinoma with signet-ring cells	9 (21.43%)	12 (28.57%)	
Lauren Classification			0.607
Intestinal	6 (14.29%)	5 (11.90%)	
Diffuse	27 (64.29%)	24 (57.14%)	
Mixed	9 (21.42%)	13 (30.96%)	
HER-2 Status			0.708
Positive	13 (30.95%)	16 (38.10%)	
Negative	26 (61.90%)	22 (52.38%)	
Unknown	3 (7.15%)	4 (9.62%)	
First-line Anti-HER-2 Therapy	10 (23.81%)	14 (33.33%)	0.469
Metastatic Sites			
Liver metastasis	18 (42.86%)	12 (28.57%)	0.255
Lymph node metastasis	28 (66.67%)	24 (57.14%)	0.501
Peritoneal metastasis	13 (30.95%)	16 (38.10%)	0.647
Number of Metastatic Organs			0.588
1	7 (16.67%)	10 (23.81%)	
≥ 2	35 (83.33%)	32 (76.19%)	
PD-L1 Expression (Combined Positive Score)			0.835
< 1	7 (16.67%)	6 (14.29%)	
≥ 1	14 (33.33%)	17 (40.48%)	
Unknown	21 (50.00%)	19 (45.23%)	
First-line Immunotherapy	14 (33.33%)	17 (40.48%)	0.652

calculated at 42.85% in the observation group and 38.09% in the control group, with no statistically significant difference ($P > 0.05$). The DCR reached 85.71% in the observation group and 75.57% in the control group, again without significant difference ($P > 0.05$). Overall, the short-term treatment efficacy between the two groups showed no meaningful statistical variation (Table 2, Figure 1).

Table 2 Comparison of Treatment Efficacy Between the Two Groups

Group	CR	PR	SD	PD	ORR	DCR
Observation Group (n=42)	2 (4.76%)	16 (38.10%)	18 (42.86%)	6 (14.29%)	18 (42.85%)	36 (85.71%)
Control Group (n=42)	1 (2.38%)	15 (35.71%)	17 (40.48%)	9 (21.43%)	16 (38.09%)	33 (75.57%)
P-value					0.824	0.570

Abbreviations: ORR, Objective Response Rate; DCR, Disease Control Rate; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.

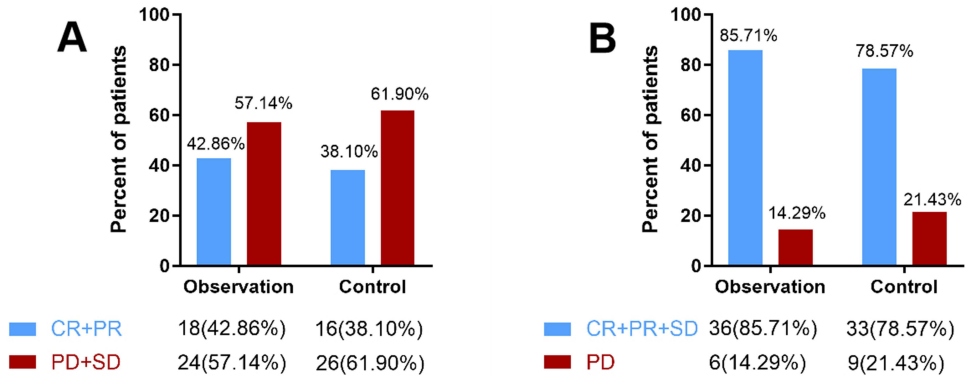

Figure 1 Efficacy Comparison Between the Two Treatment Groups. (**A**) Objective Response Rate (ORR); (**B**) Disease Control Rate (DCR).
Abbreviations: CR, Complete Response; PR, Partial Response; PD, Progressive Disease; SD, Stable Disease.

Correlation Analysis Between Treatment Protocol and Adverse Events

The analysis revealed no statistically significant differences in the incidence of adverse reactions between the observation and control groups. This included events such as hepatic impairment, hematologic toxicity, hand-foot syndrome, hypothyroidism, gastrointestinal disturbances, cardiotoxicity, and immune-related pneumonitis ($P > 0.05$). The total incidence of adverse events was 78.57% in the observation group, with a grade 3–4 adverse event incidence of 23.81%, compared to 59.52% and 11.90%, respectively, in the control group. No statistically significant differences were observed in the incidence of adverse events at any grade between the two groups (all $P > 0.05$, see Tables 3 and 4). In conclusion, the addition of Sintilimab to the therapeutic regimen did not result in a statistically significant increase in the overall incidence or severity of adverse events. Nonetheless, the trend toward a higher frequency of grade 3–4 toxicities in the observation group suggests a need for vigilant monitoring to mitigate potential cumulative safety concerns.

Table 3 Adverse Reactions in the Two Groups

Adverse Reaction Type	Observation Group (n=42)		Control Group (n=42)		*P*-value
	I-II	III-IV	I-II	III-IV	
Hepatic dysfunction	5 (11.90%)	2 (4.76%)	4 (9.52%)	1 (2.38%)	0.757
Hematologic toxicity	5 (11.90%)	3 (7.14%)	7 (11.90%)	3 (7.14%)	0.791
Hand-foot syndrome	4 (9.52%)	1 (2.38%)	2 (7.14%)	1 (2.38%)	0.713
Hypothyroidism	3 (7.14%)	0 (0%)	2 (4.76%)	0 (0%)	> 0.999
Gastrointestinal toxicity	5 (11.90%)	0 (0%)	3 (7.14%)	0 (0%)	0.713
Cardiotoxicity	2 (0%)	2 (2.38%)	2(7.14%)	0 (0%)	0.676
Immune-related pneumonitis	0 (0%)	2 (2.38%)	0 (0%)	0 (0%)	0.494
Total immune-related adverse reactions	11 (23.81%)		9 (21.43%)		0.798

Table 4 Comparison of Adverse Reaction Grades Between the Two Groups

Category	Observation Group (n=42)	Control Group (n=42)	*P*-value
Grade 1–2	23 (54.76%)	20 (45.23%)	0.663
Grade 3–4	10 (23.81%)	5 (11.90%)	0.380
Total Adverse Reactions	33 (78.57%)	25 (59.52%)	0.098

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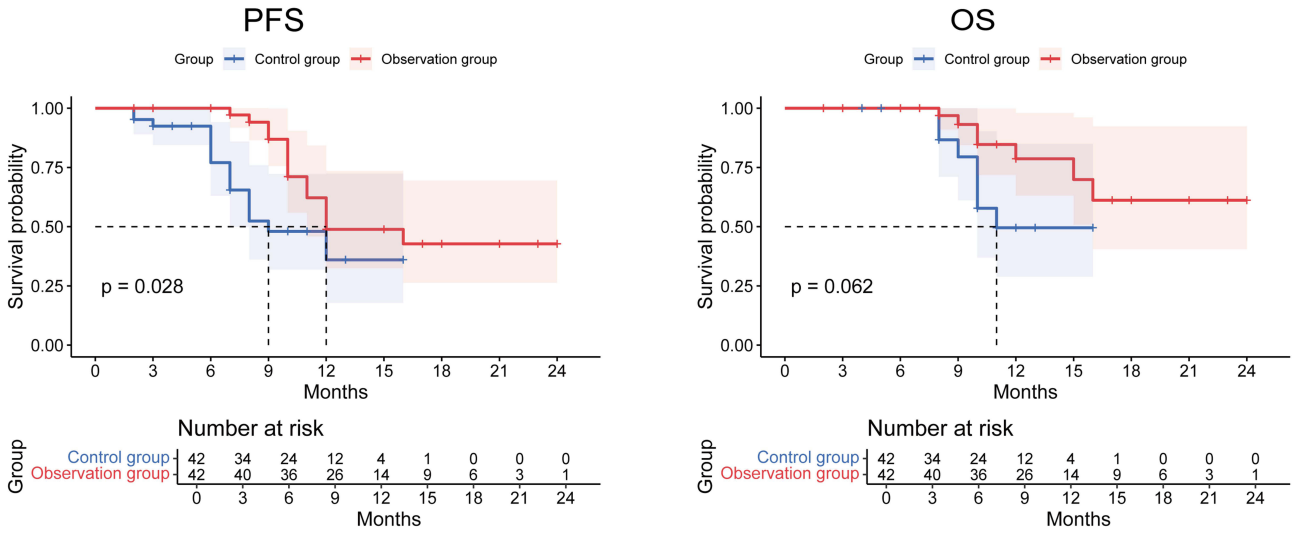

Figure 2 Comparative Analysis of PFS and OS Survival Curves Between Treatment Groups.
Abbreviations: PFS, progression-free survival; OS, overall survival. $P < 0.05$ indicates a statistically significant difference between the survival curves of the two groups.

Correlation Analysis of Therapeutic Protocols with PFS and OS Outcomes

As of the follow-up cutoff date of June 30, 2024, with a median follow-up of 8.0 months (range: 2–24 months), the median PFS was 12.0 months (95% confidence interval [CI]: 6.857–17.143 months) in the observation group and 9.0 months (95% CI: 5.668–12.332 months) in the control group. The Log rank test indicated a statistically significant difference in PFS between the two groups ($P = 0.028$; hazard ratio (HR) 0.455, 95% CI: 0.217–0.956). The median OS was 11.0 months (95% CI: 10.00–NA) in the control group, while it was not reached in the observation group. The Log rank test showed no statistically significant difference in OS between the groups ($P = 0.062$; HR = 0.384, 95% CI: 0.131–1.125). The corresponding Kaplan-Meier survival distributions are presented in Figure 2.

Discussion

Currently, second-line treatment for advanced gastric or gastroesophageal junction adenocarcinoma continues to faces numerous challenges. Studies investigating the use of ICIs in combination with chemotherapy and anti-angiogenic therapy as second-line treatment remain limited, and the findings reported thus far are inconsistent. This retrospective study analyzed advanced gastric cancer cases, comparing immune-combination therapy with chemotherapy plus anti-angiogenic therapy, aiming to provide evidence-based support for second-line treatment of advanced gastric cancer and to contribute new real-world data to a research landscape that has predominantly focused on first- or third-line therapy and dual-agent regimens. These findings offer a new strategic perspective for clinical second-line treatment, with clear clinical relevance and innovative value.

Chemotherapy not only kills tumor cells through cytotoxic effects but also modulates the tumor microenvironment, exhibiting synergistic effects with ICIs.[25] Compared with fluorouracil, paclitaxel is more likely to induce ICD.[26] In addition, combining anti-angiogenic therapy with standard chemotherapy has demonstrated encouraging therapeutic outcomes. Studies have shown that, compared to chemotherapy alone, this combination significantly enhances OS and PFS.[27]

In the treatment of gastric cancer, anti-PD-1 monoclonal antibodies, chemotherapy, and anti-angiogenic agents each demonstrate certain efficacy, but the effectiveness of monotherapy remains limited. Consequently, growing research has explored the combination of these modalities in second-line therapy to enhance therapeutic outcomes. Combining chemotherapy with anti-PD-1 inhibitors and anti-angiogenic drugs may partially overcome the limitations of monotherapy, improving treatment efficacy and survival rates.[28] Therefore, this study compared and analyzed the efficacy of anti-PD-1 monoclonal antibodies combined with anti-angiogenesis agents plus chemotherapy versus chemotherapy combined with anti-angiogenesis agents. Although no statistically significant difference was found in short-term efficacy (ORR and DCR) between the observation and control groups, the observation group showed a numerical advantage

(ORR 42.85% vs. 38.09%, DCR 85.71% vs. 75.57%), suggesting potential benefits of the immune combination therapy. This finding aligns partially with previous studies: previous immunotherapy trials for gastric cancer in later-line treatment often reported response rates of 10–20% for single-agent therapies, whereas in this study, the ORR of the combination therapy exceeded this threshold, likely due to the synergistic effect between ICIs, chemotherapy, and anti-angiogenesis agents. However, the lack of statistical significance may be attributed to a limited sample size and short follow-up duration. Safety analysis revealed that sintilimab combination therapy did not significantly increase severe toxicity risks ($P > 0.05$), though the incidence of grade 3–4 adverse events was higher in the observation group (23.81% vs. 11.90%). Given the generally poor physical condition and limited tolerance to toxicity among advanced gastric cancer patients, close monitoring of cumulative grade 3–4 toxicity risks remains clinically warranted.

Referencing FDA guidelines on clinical endpoints in advanced solid tumors, PFS serves as an early efficacy indicator with moderate-to-weak correlation to OS. The significantly prolonged PFS in the observation group (9.0 months, 95% CI: 7.698–10.302) versus the control group (7.0 months, 95% CI: 5.246–8.754; $P = 0.042$) may signal potential OS benefits, though extended follow-up is required for validation. This result is consistent with the findings of a phase II clinical trial, which confirmed that the regimen of albumin-bound paclitaxel combined with sintilimab and apatinib exhibited promising anti-tumor activity and manageable safety,[29] suggesting that the addition of sintilimab can effectively control disease progression, which is of significant importance for improving patients' quality of life and guiding subsequent treatment choices. The median OS was not reached in the observation group, and no statistical difference in OS was observed between the two groups ($P = 0.138$). This may be related to confounding factors such as insufficient follow-up time and differences in subsequent treatment regimens. Long-term survival benefits still require validation through longer follow-up. Nonetheless, the improvement in PFS offers strong support for the clinical use of sintilimab in combination therapy.

The comparison of this study with previous research further highlights its innovation. Previous gastric cancer immunotherapy studies primarily focused on first-line or third-line treatments, while this study concentrated on second-line therapy, filling the evidence gap in this field. In terms of treatment regimen, this study employed the "immune + anti-angiogenesis + chemotherapy" triple combination, complementing the "immune + chemotherapy" regimen used in studies such as CheckMate-649,[30] offering more options for clinical practice. This investigation has several limitations. First, its single-center, small-sample (n = 84) design resulted in insufficient statistical power, which may affect the assessment of long-term endpoints such as OS and the generalizability of the results. Second, the selection of treatment regimens and the division into observation and control groups relied on clinicians' decisions and individual patient factors such as disease status and treatment preferences, inevitably introducing selection bias and reducing the objectivity of between-group comparisons. Finally, the lack of biomarker subgroup analyses, such as PD-L1 expression, prevented the identification of predictive efficacy factors. Future research should involve multicenter, prospective, randomized controlled trials with larger sample sizes, incorporating biomarker-guided precision treatment strategies to further optimize combination regimens.

The results of this study demonstrate that the regimen combining anti-PD-1 monoclonal antibodies with chemotherapy and anti-angiogenic agents shows preliminary efficacy and manageable safety in the second-line treatment of advanced gastric cancer. The significant prolongation of mPFS in the observation group provides a reference for optimizing second-line treatment strategies for advanced gastric cancer. However, attention must be given to the cumulative risk of immune-related adverse events, and individualized treatment strategies should be employed to optimize the efficacy-toxicity balance. Future studies should focus on the exploration of predictive efficacy biomarkers, optimization of combination therapy regimens, and validation of long-term survival benefits to advance gastric cancer immunotherapy.

Data Sharing Statement

Data is available from the corresponding author on request.

Ethics Statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by Affiliated Hospital of Hebei University (No.201908HB30).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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