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Efficacy and safety of anti-PD-1 antibodies plus small molecule anti-angiogenic drugs and chemotherapy in gastric cancer peritoneal metastasis: a multicenter real-world study

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Abstract

Background Immunotherapy combined with chemotherapy has emerged as the first-line standard treatment for advanced gastric cancer. However, obvious survival benefits in patients with peritoneal metastatic gastric cancer remain elusive. The combination of anti-angiogenic agents and immunotherapy has shown synergistic effects. However, currently there are no relevant reports on the efficacy and safety of immunotherapy combined with anti-angiogenic agents and chemotherapy in patients with gastric cancer peritoneal metastatic.

Methods We conducted a multicenter, retrospective clinical study in four independent healthcare facilities, enrolling advanced gastric cancer patients with peritoneal metastatic who received immunotherapy in combination with anti-angiogenic agents and chemotherapy between January 2020 and March 2023. All patients were treated with triple combination regimen for at least two and up to eight cycles before being adjusted for immunotherapy and targeted therapy. This study observed overall survival (OS) and time to treatment failure (TTF), as well as an exploratory analysis of the impact of ascites and peritoneal metastases on the prognosis of all patients.

Results This study enrolled 30 eligible patients in the final analysis cohort. The median TTF and OS were 7.03 months [95% confidence interval (CI), 4.17–9.89] and 13.33 months (95% CI: 10.96–15.71), respectively. The 6-month and 12-month OS rates were 83.0% and 53.0%, respectively. The objective response rate (ORR) was 58.3%, and the disease control rate (DCR) was 83.3% in 12 patients who were evaluated for response with at least one measurable lesion. Exploratory subgroup analysis revealed that the median TTF and OS in the subgroup without ascites were significantly better than those in the subgroup with ascites, with a median TTF of 9.03 vs. 4.63 months ($\chi^2=8.579$, $P=0.003$), and median OS of 17.83 vs. 11.87 months ($\chi^2=6.155$, $P=0.013$). Conversely, the extent of peritoneal metastasis had little effect on TTF and OS. The common adverse reactions were leukopenia (46.67%), neutropenia (43.33%),

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fatigue (36.67%), anemia (36.67%), decreased appetite (36.67%), thrombocytopenia (33.33%), and hypertension (33.33%). No new safety signals were observed.

Conclusions The combination of immunotherapy, anti-angiogenic agents, and chemotherapy demonstrated therapeutic potential with a manageable safety profile in patients with peritoneal metastatic gastric cancer. These findings should be interpreted cautiously due to the inherent limitations of retrospective analyses and need to be validated through prospective randomized controlled trials to establish clinical efficacy and optimize patient selection criteria.

Keywords Gastric cancer peritoneal metastasis, Immunotherapy, Anti-angiogenic agents, Chemotherapy, Retrospective study

Introduction

Due to the prevalence of gastric cancer among the world, most patients suffered from its high risk of recurrence and metastasis, as well as the same circumstances in china [1, 2]. Peritoneal metastasis was the typical characteristic of poor prognosis in advanced gastric cancer patients with only 3–6 months median OS and less than 2% 5-year survival rate. Almost 20% gastric cancer patients were initially diagnosed with peritoneal metastasis and approximately 50% with developed peritoneal metastasis after early radical resection [3, 4]. While the cytoreductive surgery (CRS) and the hyperthermic intraperitoneal chemotherapy (HIPEC) are applied as the treatments of gastric cancer peritoneal metastasis [5–7], however, their safety and efficacy remain controversial. Thus, safer and more effective treatment options are sought urgently.

Recently, with the development of immune checkpoint inhibitors (ICIs), the anti-PD-1/PD-L1 drugs combined with chemotherapy has become the first-line standard treatment for advanced gastric cancer. This therapeutic regimen improved the median progression-free survival (PFS) to 7–9 months and the median OS to 14–16 months [8–11]. However, emerging clinical evidence reveals significant limitations of this regimen in gastric cancer peritoneal metastases (GCPM), and pivotal trials show inconsistent outcomes in GCPM. As reported in ATTRACTION-4 [12], no OS benefit was observed in the peritoneal metastasis subgroup of gastric cancer treated with nivolumab monotherapy combination with chemotherapy. In the RATIONALE 305 study, there was an improvement in OS with the combination of immunotherapy and chemotherapy, irrespective of the presence of peritoneal metastases. However, the subgroup with peritoneal involvement exhibited limited benefit [8]. A growing body of research has highlighted the unique immune microenvironment of peritoneal metastases from gastric cancer. It has been revealed that peritoneal metastases are characterised by vascular abnormalities and the absence of immune effector cells, a substantial increase in Tregs and M2 macrophages leading to an immunosuppressive dominance, and hypoxia suppressing

antigen presentation and CD8 + T-cell activity [13–16]. This immunosuppressive microenvironment may, therefore, account for the limited benefit from immune-combination chemotherapy in patients with GCPM.

A number of preclinical studies have indicated that anti-angiogenic therapy can induce the normalisation of tumour vasculature, improve infiltration of immune cells within the tumour, and strengthen their cytotoxic effects. Furthermore, it has been demonstrated that this therapy promotes the polarisation of tumour-associated macrophages (TAMs) from the M2 to the M1 phenotype, thus reprogramming the immune microenvironment. Consequently, the combination of anti-angiogenic therapy and immunotherapy has the potential to enhance the efficacy of immunotherapy [17–21]. In a clinical study in hepatocellular liver cancer, it was further demonstrated that anti-angiogenic therapy reduces regulatory T cells (Treg) and myeloid inflammatory cells, cooperates with PD-L1 antibodies to enhance anti-tumour immunity [22]. The SPACE study which conducted in 2020 demonstrated that first-line chemotherapy combined with apatinib and camrelizumab achieved a 76.5% objective response rate and 8.4-month median progression-free survival in advanced gastric cancer patients, and it observed immune microenvironment changes, including fewer FOXP3 + T-cells and M2 type TAMs, and more PD1 + cells and M1 type TAMs [23]. These findings reveal the mechanism of synergistic anti-tumour effects of triple therapy by remodelling the immunosuppressive microenvironment, and provide a theoretical basis for combining anti-angiogenic drugs with immunotherapy and chemotherapy to overcome biological barriers such as gastric cancer peritoneal metastasis (GCPM). Based on this mechanistic advantage, clinical studies have demonstrated the potential for this triple modality in the treatment of various solid tumours, including non-small cell lung cancer, hepatocellular carcinoma, oesophageal cancer and gastric cancer [24–26]. However, thus far, this triple-drug regimen has not been evaluated as a safe and effective therapeutic strategy for GCPM.

We hypothesized that combining chemotherapy and immunotherapy, along with anti-angiogenic drugs may

improve the prognosis of patients with peritoneal metastatic gastric cancer. Consequently, we conducted this multicenter, retrospective clinical study to explore the efficacy and safety of a triple combination therapy of immunotherapy, anti-angiogenic agents, and chemotherapy in patients with peritoneal metastatic gastric cancer and to lay the groundwork for future prospective clinical studies.

Materials and methods

Study design and study patients

This retrospective clinical study was multicenter, including patients from four independent medical institutions: the Suzhou Hospital Affiliated to Nanjing Medical University (Suzhou Municipal Hospital), Jiangsu Provincial People's Hospital, Nanjing Pukou People's Hospital, and Affiliated Hospital of Jiangsu University. All enrolled patients had primary gastric cancer or adenocarcinoma of the gastroesophageal junction with peritoneal metastasis, diagnosed by histopathology. The criteria for peritoneal metastasis were as follows: 1) Peritoneal metastatic nodules confirmed by laparoscopy, open surgery, or biopsy pathology and 2) fulfilled the diagnostic criteria by enhanced computed tomography (CT) scan including irregular nodules and thickening of the peritoneum, omental cake, multiple cord shadows in fat space (mesentery, omentum, peritoneum and intestinal wall), the intestinal wall thickened, or a large amount of abdominopelvic fluid collection. Contrast-enhanced CT examinations were performed using multidetector scanners (Siemens SOMATOM Force, GE Revolution Frontier, and Philips iCT Elite) with patients in the supine position. Following a 6-h fasting period, nonionic contrast agent iohexol (350 mgI/mL) was intravenously administered through the antecubital vein at a dose of 5.3 mL/kg body weight and an injection rate of 5.1 mL/s. The diagnosis must be made by two experienced abdominal diagnostic imaging physicians.

The inclusion criteria were as follows: 1) Aged 18–75 years; 2) histopathologically confirmed diagnosis of gastric cancer or adenocarcinoma of the gastroesophageal junction; 3) confirmation of peritoneal metastasis by laparoscopy or imaging at the initiation of treatment; 4) Eastern Cooperative Oncology Group performance status of 0–1; 5) first-line use of PD-1 immune checkpoint inhibitors combined with anti-angiogenic drugs and chemotherapy, with a minimum of two treatment cycles; 6) hematological criteria: hemoglobin ≥ 80 g/L, absolute neutrophil count $\geq 1.5 \times 10^9$ /L, platelet count $\geq 80 \times 10^9$ /L, alanine aminotransferase, and aspartate aminotransferase $\leq 2.5 \times$ upper limit of normal (ULN), serum total bilirubin $\leq 1.5 \times$ ULN, estimated glomerular filtration rate ≥ 60 mL/min (Cockcroft-Gault formula);

7) clinical life expectancy of patients aged ≥ 3 months; 8) complete clinical case data, laboratory test results, and follow-up data.

The exclusion criteria were as follows: 1) Immunotherapy combined with anti-angiogenesis targeted therapy and chemotherapy was used as second-line treatment or above; 2) patients received peritoneal thermal perfusion chemotherapy during the treatment period; 3) accompanied by intestinal obstruction at the time of first treatment; 4) any hemorrhagic event with a severity grade of three or more on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE 5.0) within four weeks before the first treatment; 5) the existence of a hypertensive crisis before the first treatment or a combination of drugs to lower blood pressure could not be controlled within the normal range; 6) severe dysfunction of heart, liver, and kidney or previous history of cardiovascular and cerebrovascular diseases and are still taking oral thrombolytic or anticoagulant drugs; 7) patients with immunodeficiency disorders; 8) patients with active autoimmune diseases or a history of autoimmune diseases that may relapse are on systemic immunosuppressive treatment; 9) allergy to active ingredients or excipients of therapeutic drugs.

Treatment and evaluation of therapeutic efficacy

The enrolled patients were treated with a triple regimen of PD-1 inhibitor immunotherapy combined with anti-angiogenesis-targeted therapy and chemotherapy. The PD-1 inhibitors primarily included tislelizumab (200 mg, intravenous drips (IVD), every 3 weeks), sintilimab (200 mg, IVD, every 3 weeks), camrelizumab (200 mg, IVD, every 3 weeks), and nivolumab (240 mg, IVD, every 3 weeks). The targeted anti-angiogenesis drugs primarily comprised anlotinib (8–12 mg orally, once daily for days 1–14, every 3 weeks) and apatinib (250 mg orally, once daily). The chemotherapy regimens included XELOX (capecitabine 800 mg/m² orally, twice daily for days 1–14, oxaliplatin 130 mg/m² IVD on day 1, every 3 weeks), SOX (Tegafur, Gimeracil, and Oteracil Potassium Capsules 40 mg/m² orally, twice daily for days 1–14, oxaliplatin 130 mg/m² IVD on day 1, every 3 weeks), and single-agent albumin-bound paclitaxel (260 mg/m² IVD on day 1, every 3 weeks).

During each treatment cycle, symptomatic management and medication dosage adjustments were made in response to treatment-related adverse events. If the patient well tolerated the treatment, the triple therapy regimen was adjusted to immunotherapy combined with targeted anti-angiogenesis maintenance therapy after 6–8 cycles until disease progression, intolerable adverse events, discontinuation at the patient's request, or the physician's discretion. Detailed history, physical

examination, and laboratory tests (complete blood count, urinalysis, liver and kidney function tests, and tumor markers CA125, CEA, and CA153) were conducted before each treatment cycle, and tumor evaluation was performed using thoracic and abdominopelvic CT scans at intervals of 2–3 cycles.

The amount of ascites was assessed by computed tomography at pretreatment baseline [27], with cases stratified as none, small (within the pelvic), or moderate (beyond the pelvic cavity). In this study, small and moderate of ascites were combined into the ascites group. Peritoneal metastasis was categorized by the Japanese Research Society for Gastric Cancer as follows [27]: P1, metastatic nodules confined to the peritoneum adjacent to the stomach; P2, several scattered metastatic nodules within the peritoneal cavity; P3, multiple diffuse metastatic nodules throughout the peritoneal cavity. As it was difficult to distinguish between P2 and P3 on imaging, they were included in the P2/P3 group for this study.

Study endpoints

The primary endpoint was OS, which refers to the date of treatment to the date of death from any cause. For patients still alive at the time of the last follow-up, OS was recorded as data censored. The secondary endpoints were safety, TTF, 6-month survival rate, 12-month survival rate, ORR, and DCR.

Safety refers to any adverse events in patients during clinical studies, including clinical symptoms and abnormal laboratory test results. Adverse events were graded according to the NCI-CTCAE 5.0. TTF refers to the duration from the first day of the patient's treatment regimen to the time of treatment regimen change or death for any reason. The clinical physician may determine the reason for changing the regimen based on tumor markers, clinical symptoms, imaging assessments of disease progression, or because the patient cannot tolerate toxic side effects. For patients with measurable lesions at baseline, efficacy assessment was conducted according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, categorizing responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ORR refers to the proportion of patients evaluated as having a complete or partial response, whereas DCR refers to the proportion of patients evaluated as having a CR, PR, or SD.

Patients will be followed up through outpatient visits, regular hospitalizations, or telephone messages until the patient's death or the last follow-up date of this study (May 31, 2023).

Statistical methods

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 26.0; IBM Corp, Armonk, New York, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD), and categorical data are presented as percentages (%). Survival analysis was performed using the Kaplan–Meier method, and survival curves were plotted. The significance of the differences was tested using the log-rank test. All statistical tests were two-sided, and a p -value < 0.05 was considered statistically significant.

Results

Patient characteristics

Between January 2020 and March 2023, 236 patients with gastric cancer or gastroesophageal junction adenocarcinoma accompanied by peritoneal metastasis were screened. Ultimately, 30 valid cases were included in the analysis cohort (Fig. 1).

The median age of all patients was 62.5 (range 41–73) years, with 23 males and 7 females. Nine of these cases were definitively peritoneal metastases by laparoscopic exploration, 20 were diagnosed as peritoneal metastases by imaging examination, and one was confirmed to have peritoneal metastasis through laparotomy. Apart from peritoneal metastasis, the most common sites of distant metastasis among the 30 patients were non-regional lymph node metastasis (53.33%) and liver (26.67%). Regarding tissue differentiation, 22 cases (73.33%) were undifferentiated or poorly differentiated, three cases were moderately differentiated, and the degree of differentiation was unknown in another five cases. Immunohistochemical testing for PD-L1 was performed in 15 patients, of which 80% (12 patients) tested negative, and three cases had PD-L1 combined positive score (CPS) of 5, 3, and 1, respectively. The detailed baseline characteristics of the enrolled patients are presented in Table 1.

Efficacy

The median follow-up for all enrolled patients as of May 31, 2023, was 15.33 months (95% CI: 12.59–18.07). The median number of cycles treated with the above regimen was 6.50 (3–22 cycles). The OS rates were 83.0% and 53.0% at 6 and 12 months, respectively. The median OS and median TTF were 13.33 months (95% CI: 10.96–15.71) and 7.03 months (95% CI: 4.17–9.89), respectively (Figs. 2A–B).

Exploratory analyses

Regarding the analysis of peritoneal metastasis extent, the findings indicate that the median TTF for the P1 subgroup was 8.93 months (95% CI: 5.09–12.77), higher

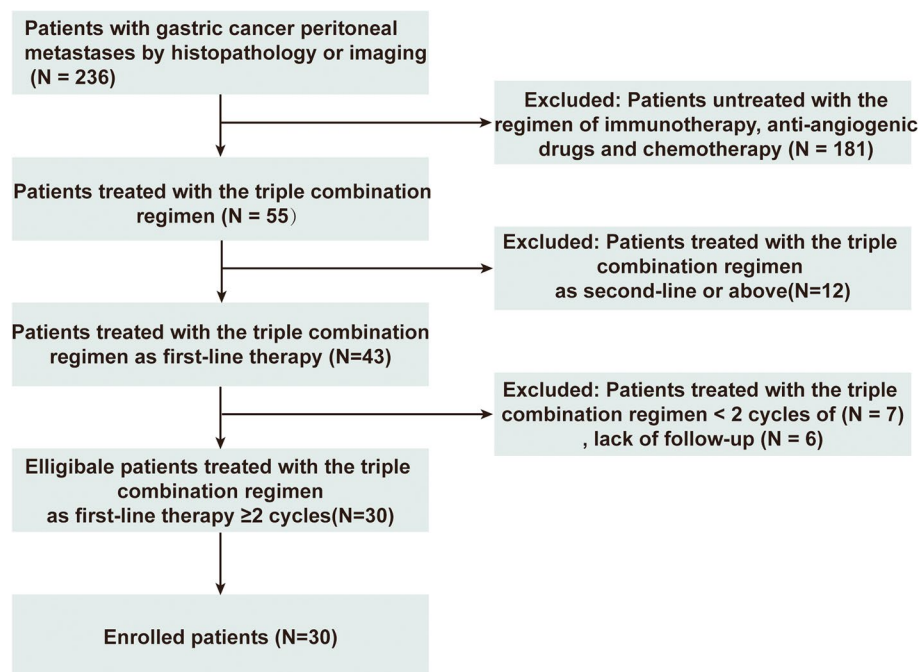


Fig. 1 Patient selection flowchart

than the 6.53 months (95% CI: 1.94–11.12) for the P2/P3 subgroup. However, the log-rank test between the two groups did not reach statistical significance ($\chi^2 = 3.077$, $P = 0.079$; Fig. 3A). The median OS was 13.33 months (95% CI: 7.98–18.68) in the P1 subgroup and 11.97 months (95% CI: 9.06–14.88) in the P2/P3 subgroup. The log-rank test between the two groups did not reach statistical significance ($\chi^2 = 0.953$, $P = 0.329$; Fig. 3B).

However, when analyzing the ascites situation, it was observed that the median TTF for the non-ascites subgroup was 9.03 months (95% CI: 6.65–11.41), compared to 4.63 months (95% CI: 2.20–7.06) for the ascites subgroup. Additionally, the median OS for the non-ascites subgroup was significantly better than that of the ascites subgroup, at 17.83 months (95% CI: 9.81–25.85) and 11.87 months (95% CI: 7.22–16.52) respectively, with both differences being statistically significant ($\chi^2 = 8.579$, $P = 0.003$; $\chi^2 = 6.155$, $P = 0.013$; Figs. 3C–D).

Objective response rate and disease control rate

Of the 30 patients, 12 had measurable and evaluable lesions during pretreatment examinations, and all patients completed at least one tumor evaluation after treatment. There were no cases of CR, seven of PR, three of SD, and two of PD, yielding an objective response rate of 58.3% and a disease control rate of 83.3%. Detailed information on the tumor response is provided in Fig. 4.

Toxicity assessment

All enrolled patients experienced treatment-related adverse event (TRAE) of any grade, with no fatal adverse drug reactions observed according to CTCAE v5.0 criteria. The common adverse reactions were leukopenia (46.67%), neutropenia (43.33%), fatigue (36.67%), anemia (36.67%), decreased appetite (36.67%), thrombocytopenia (33.33%), and hypertension (33.33%). Most of them had a grade 1–2 severity. Furthermore, dose was decreased in 26.67% (8/30) of the patients mainly due to leukopenia (4/30), transaminase elevation (2/30), thrombocytopenia (1/30), vomiting (1/30). No treatment-related deaths or new safety signals were observed. The detailed results are presented in Table 2.

Discussion

This is the first clinical retrospective, multi-center study of anti-PD-1 antibody combined with chemotherapy and anti-angiogenic targeted therapy for untreated gastric cancer peritoneal metastasis. In our study, we observed the median OS of 13.33 months (95% CI: 10.96–15.71) and the median TTF of 7.03 months (95% CI: 4.17–9.89). Moreover, exploratory subgroup analysis revealed that ascites were associated with a poorer prognosis.

Current evidence suggests that immunotherapy provides limited clinical benefit in GCPM, with existing study data showing inconsistent results [8, 12]. Successful immunotherapy requires not only the infiltration of

Table 1 Baseline demographic and clinical characteristics of patients

Characteristics	N = 30 patients (%)
Age (year)	
Median (range)	62.5 years (41–73 years)
Gender	
Male	23 (76.67%)
Female	7 (23.33%)
Diagnostic methods of peritoneal metastasis	
Laparoscopic exploration	9 (30.00%)
Open laparotomy	1 (3.33%)
Radiographic examination	20 (66.67%)
Extent of peritoneal metastasis	
P1	11 (36.67%)
P2/P3	19 (63.33%)
Number of distant metastatic organs other than peritoneal metastases	
0	9 (30.00%)
1–2	18 (60.00%)
≥ 3	3 (10.00%)
Degrees of histologic differentiation	
Un and low differentiated adenocarcinoma	22 (73.33%)
Moderate and highly differentiated adenocarcinoma	3 (10.00%)
Unknown	5 (16.67%)
Lauren classification	
Intestinal	9 (30.00%)
Diffuse	14 (46.67%)
Unknown	7 (23.33%)
ascites of initial treatment	
No	12 (40.00%)
Yes	18 (60.00%)
Common distant metastatic site	
Peritoneum	30 (100.00%)
Non-regional lymph node	16 (53.33%)
Liver	8 (26.67%)
Lung	1 (3.33%)
Bone	1 (3.33%)
Adrenal gland	2 (6.67%)
HER2 status	
Negative	20 (66.67%)
Positive	1 (3.33%)
Unknown	9 (30.00%)
MMR or MSI status	
pMMR or MSS	18 (60.00%)
dMMR or MSI-H	0 (0.00%)
Unknown ^a	12 (40.00%)
Combined Positive Score of PD-L1 expression	
< 1	12 (40.00%)
≥ 1	3 (10.00%)
Unknown ^a	15 (50.00%)
PD-1 inhibitors	
Tirelizumab	8 (26.67%)
Carrelizumab	16 (53.33%)

Table 1 (continued)

Characteristics	N= 30 patients (%)
Nivolumab	2 (6.67%)
Sintilimab	4 (13.33%)
Anti-angiogenic small molecule drugs	
Anlotinib	11 (36.67%)
Apatinib	19 (63.33%)
Chemotherapy regimen	
XELOX regimen	6 (20.00%)
SOX regimen	18 (60.00%)
Albumin-bound paclitaxel	6 (20.00%)

Abbreviations: *pMMR* mismatch repair proficient, *MSS* Microsatellite stable, *dMMR* Mismatch repair deficiency, *MSI-H* Microsatellite instability-high, *HER2* Human Epidermal growth factor Receptor 2, *XELOX* Capecitabine plus oxaliplatin, *SOX* Tegafur, Gimeracil and Oteracil Potassium Capsules plus oxaliplatin

^a PD-L1 testing and MSI have not been routinely performed due to insufficient availability of biopsy tissue and lack of mandatory clinical requirements

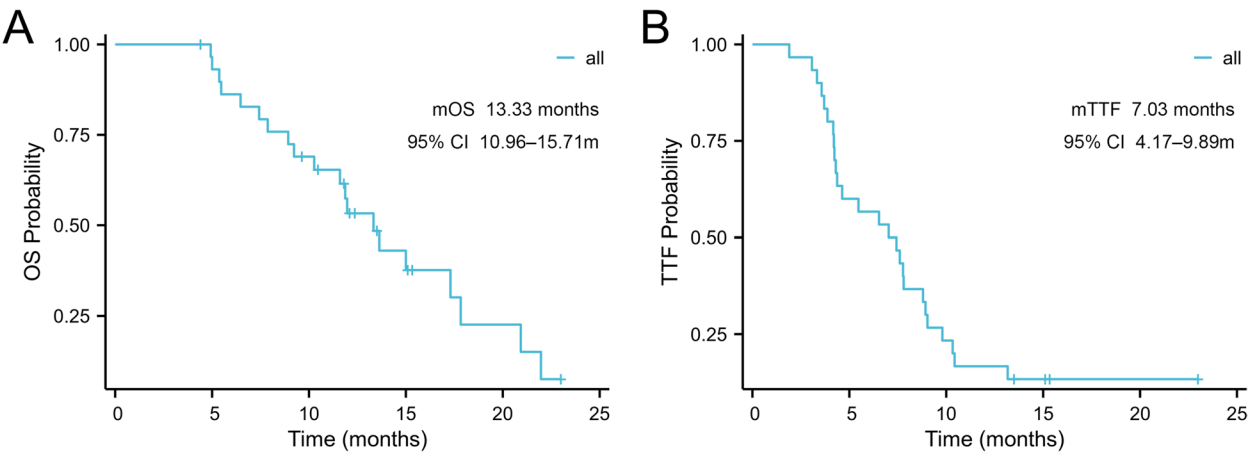


Fig. 2 Kaplan–Meier survival curves. **A** The median OS was 13.33 months (95% CI: 10.96–15.71). **B** The median TTF was 7.03 months (95% CI, 4.17–9.89). * Short vertical lines on the survival curve indicate censored data

immune cells but also an immune-supportive micro-environment to maintain the proliferation and function of T cells. Some studies have found that T-cell immune function is significantly depleted during the process of GCPM, with a significant increase in immature or immunosuppressive phenotypes. Additionally, the number of dendritic cells (DCs) increases, and they exhibit reduced antigen presentation ability, promote tumor angiogenesis, and significantly increase immune suppression levels in the tumor microenvironment with peritoneal metastasis [13, 28–30]. In the CheckMate-649 study, approximately 60% of the population exhibited a PD-L1 CPS ≥ 5 , and the subgroup with a higher PD-L1 CPS expression showed significant benefits [9]. In our study, 15 patients underwent PD-L1 testing, and the results showed that 80.00% of the patients tested negative, with only 6.67% (one case) showing CPS ≥ 5 and 13.33% (two cases) of patients with CPS between 1 and 5. Current evidence

regarding PD-L1 expression differences between GCPM and non-peritoneal metastases remains insufficient. Despite the restricted sample size of our study, which precludes the drawing of definitive conclusions. But several studies suggest that GCPM possesses a distinctive immune profile. The immune microenvironment of GCPM is characterised by a stromal-myeloid ecological niche, which is dominated by an enrichment of SPP1 + tumour-associated macrophages (TAMs) and THBS2 +stromal carcinoma-associated fibroblasts (mCAFs), along with a higher proportion of regulatory T cells (Tregs), a higher proportion of M2-type macrophages and myeloid-derived suppressor cells (MDSCs). GCPM have a different pathway and immune composition compared to liver metastases, a feature that may contribute to immune checkpoint inhibitor (ICB) resistance [13, 14, 31]. In addition, the stromal-myeloid interaction of GCPM is a central mechanism of immune resistance [14].

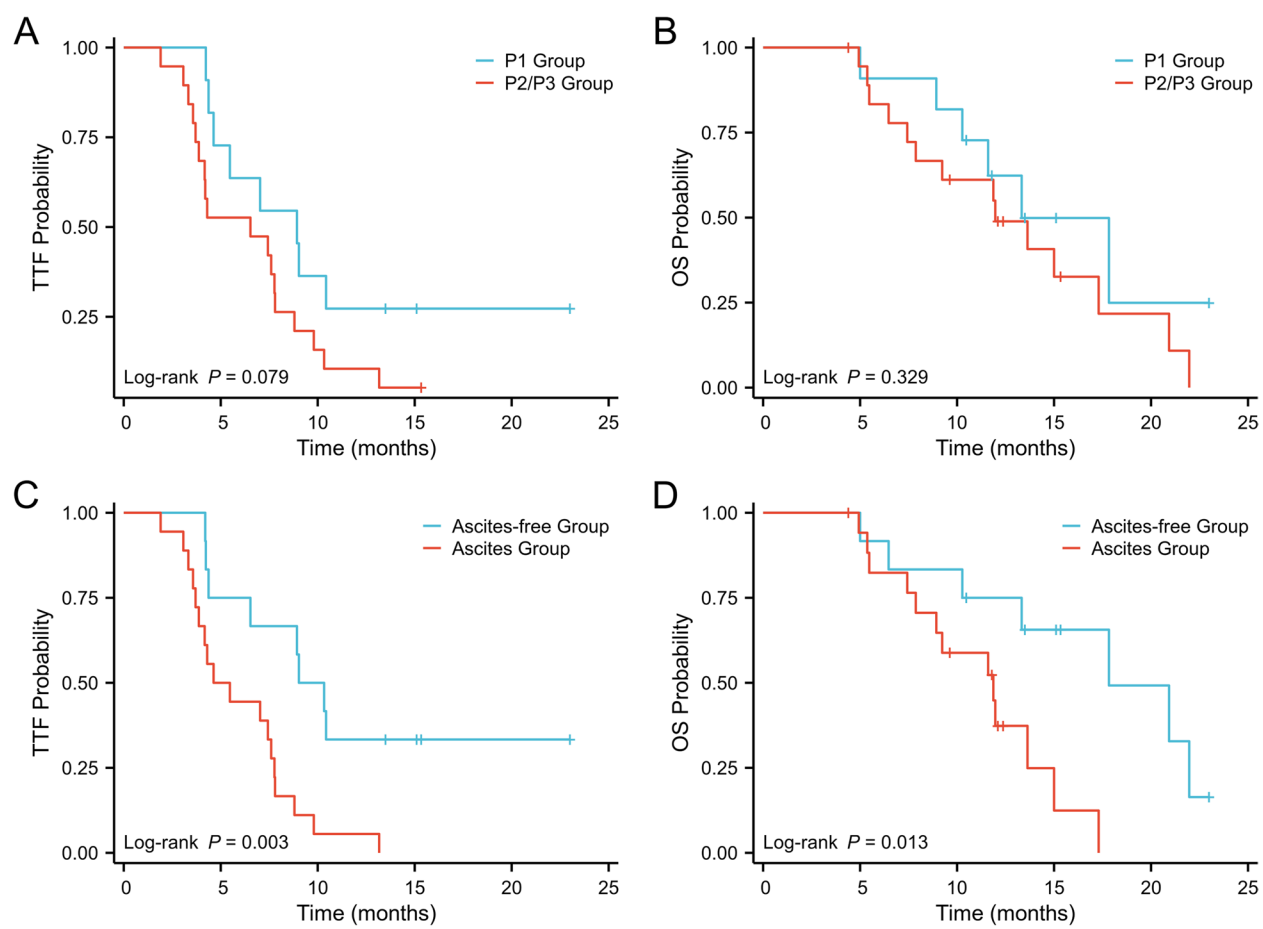


Fig. 3 **A** The median TTF for patients of subgroups P1 and P2/P3 (8.93 vs. 6.53 months) ($P = 0.079$). **B** The median OS for patients of subgroups P1 and P2/P3 (13.33 vs. 11.97 months) ($P = 0.329$). **C** The median TTF for patients of ascites-free group and ascites group (9.03 vs. 4.63 months) ($P = 0.003$). **D** The median OS for patients of ascites-free group and ascites group (17.83 vs. 11.87 months) ($P = 0.013$). * Short vertical lines on the survival curve indicate censored data

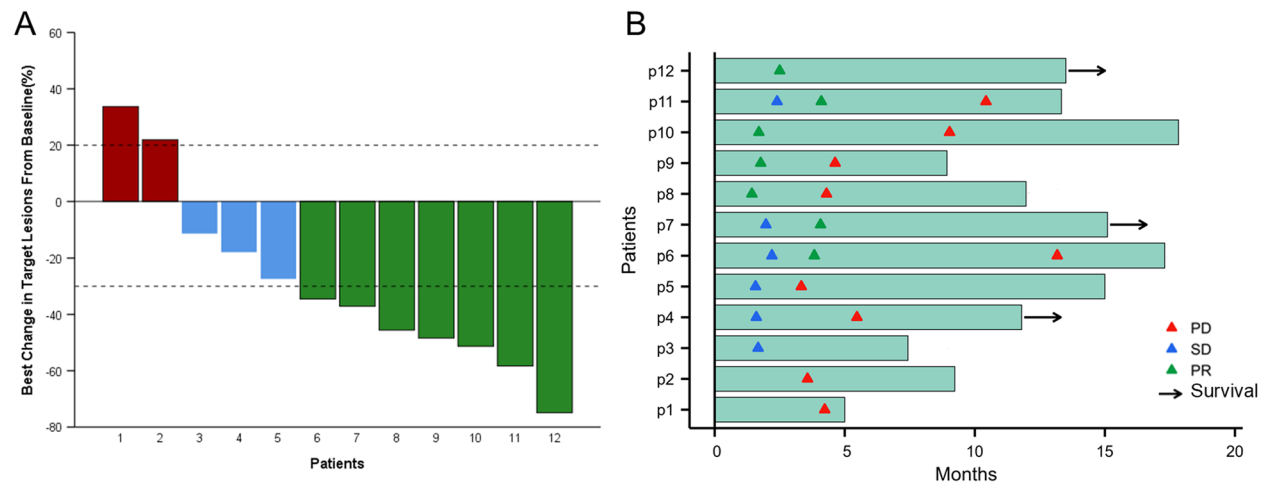


Fig. 4 Antitumor response of 12 patients **A** Waterfall plot of best percentage change from baseline in target lesion size. **B** Swimmer plot showing response duration

Table 2 Summary of treatment-related adverse events in all treated patients (N%)

Adverse events	All patients (n = 30)		
	Grade 1–2 (%)	Grade 3–4 (%)	All Grade (%)
Anemia	10 (33.33)	1 (3.33)	11 (36.67)
Leucopenia	10 (33.33)	4 (13.33)	14 (46.67)
Neutropenia	10 (33.33)	3 (10.00)	13 (43.33)
Thrombocytopenia	9 (30.00)	1 (3.33)	10 (33.33)
Transaminase elevation	5 (16.67)	1 (3.33)	6 (20.00)
Renal dysfunction	1 (3.33)	0 (0.00)	1 (3.33)
Thyroid dysfunction	5 (16.67)	0 (0.00)	5 (16.67)
Decreased appetite	11 (36.67)	0 (0.00)	11 (36.67)
Vomiting	7 (23.33)	1 (3.33)	8 (26.67)
Diarrhea	6 (20.00)	1 (3.33)	7 (23.33)
Fatigue	11 (36.67)	0 (0.00)	11 (36.67)
Hypertension	9 (30.00)	1 (3.33)	10 (33.33)
Hand-foot syndrome	7 (23.33)	0 (0.00)	7 (23.33)
Proteinuria	6 (20.00)	0 (0.00)	6 (20.00)
Neurotoxicity	9 (30.00)	0 (0.00)	9 (30.00)
Rash	2 (6.67)	2 (6.67)	4 (13.33)

Furthermore, elevated levels of IL-10 and TGF- β have been observed in the GCPM microenvironment, with these factors maintaining an immunosuppressive state by inducing Tregs differentiation and M2 macrophage polarization [13, 32]. Collectively, these characteristics contribute to the establishment of an immunosuppressive microenvironment in GCPM, which may provide a rationale for the suboptimal immune response observed in patients with peritoneal metastases of gastric cancer.

Adding targeted anti-angiogenic drugs based on immunotherapy combined with chemotherapy can further improve clinical benefits. Some studies have proposed that small-molecule anti-angiogenic drugs can inhibit tumor angiogenesis, induce normalization of tumor blood vessels, promote infiltration of effector T cells into the tumor microenvironment, and reduce the proliferation of tumor-associated immunosuppressive cells. Moreover, after the activation of effector T cells by immunotherapy, these drugs can promote the normalization of tumor blood vessels through IFN γ (Interferon gamma)-mediated vascular remodeling [17, 33, 34]. This positive feedback loop between vascular remodeling and immune stimulation can synergistically enhance efficacy. In our previous study, SPACE also found that triple combination regimen could improved the PD-1 expression in tumor immune niche and transferred the immunosuppressive condition [23]. The current combination therapy using anti-PD-1 antibodies, chemotherapy, and anti-angiogenic agents shows promising anti-tumor activity

across various tumors [35–37]. A study indicated that patients with advanced intrahepatic cholangiocarcinoma (ICC) who received the combination of teraplizumab, lenvatinib, and gemcitabine plus oxaliplatin (GEMOX) (NCT03951597) achieved a breakthrough ORR of 80%, with the OS and PFS reaching 22.5 months and 10.2 months, respectively [35]. In a separate study, Sintilimab in combination with apatinib and chemotherapy was investigated as a potential alternative treatment for patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma. The median PFS and OS were reported to be 8.5 months (95% CI, 5.4–11.5) and 12.5 months (95% CI, 3.7–21.3), respectively [36]. In peritoneal metastasis of gastric cancer, case reports have also indicated that the multimodal treatment modality of Camrelizumab in combination with apatinib and chemotherapy may result in a reduction of the grading of the primary site of gastric cancer, effective control of peritoneal metastasis, and the potential for radical resection of gastric cancer (R0 surgery). This could ultimately improve the survival of patients with gastric cancer combined with peritoneal metastasis [37]. The RATIONALE 305 study, the median OS was 11.7 months in a subgroup of patients with peritoneal metastases who underwent immunotherapy combined with chemotherapy [8], while our study observed a median OS of 13.33 months (95% CI: 10.96–15.71). Additionally, in 12 patients with measurable evaluable lesions, ORR was 58.3% and DCR was 83.3%. All patients had an acceptable safety profile during treatment, and no new serious safety signals were identified.

Malignant ascites are associated with worse prognosis in patients with advanced gastric cancer, and have no best therapeutic regimens [38]. An exploratory analysis was conducted on the impact of peritoneal metastasis and ascites on prognosis. The outcomes revealed that the median OS and TTF in the P1 subgroup were slightly higher than those in the P2/P3 subgroup. Although a trend of benefit in TTF was observed in the short term, it failed to attain statistical significance between the two groups. When analyzing the presence of ascites, the subgroup without ascites showed statistically significant advantages in both TTF and OS compared with the subgroup with ascites. In a retrospective analysis of patients with dMMR/MSI-H metastatic colorectal and gastric cancer undergoing ICI therapy, patients with peritoneal metastasis and ascites had the worst PFS and OS in the mGC cohort (2-year PFS rate: 17.7%, HR 4.57, 95% CI: 2.07–10.09, 2-year OS rate: 26.5%, HR 4.18, 95% CI: 1.70–10.26). Conversely, patients with peritoneal metastases without ascites had comparable PFS and OS to those without peritoneal metastases (2-year PFS rate: 50.2% vs. 61.4%, HR 1.48,

95% CI: 0.55–4.02, 2-year OS rate: 56.5% vs. 60.6%, HR 1.69, 95% CI: 0.55–5.18), and multivariate analysis revealed that the presence of ascites was an independent factor affecting survival [39]. Another retrospective analysis of advanced gastric cancer patients with ascites receiving nivolumab monotherapy demonstrated a significant association between high-volume ascites and inferior OS (OS: median 5.3 months [95% CI 3.4–7.3] vs. 2.5 months [95% CI 0.0–5.0] for low vs. high ascites burden) [40]. Our findings align with those of the aforementioned studies, and the presence or absence of ascites had a significant prognostic impact. However, considering the limited sample size in our cohort, further validation through large-scale, multi-center clinical trials is necessary to confirm these observations and establish robust clinical correlations.

Meanwhile, this study has several limitations. First, the study relied on retrospective data from a small patient cohort, thus limiting the level of evidence. Although the integration of multicenter data helped mitigate institution-specific biases, residual confounding factors might still influence the interpretation of the findings. Second, the absence of propensity score matching (PSM) precluded direct comparative efficacy analysis between our cohort and the immunotherapy-chemotherapy combination group. Third, accurate PCI scores were not obtained through total laparoscopic exploration, reducing the statistical validity of the relationship between peritoneal metastasis and prognosis. Prospective randomized controlled phase III trials should be prioritized to validate these findings, with patients stratified by integrated models that incorporate both clinical characteristics (e.g. PCI, ECOG status) and molecular profiles (PD-L1 CPS, HER2 expression, circulating tumor DNA). Furthermore, conducting parallel spatial multi-omics analyses (single-cell RNA-seq, spatial transcriptomics, multiplex immunofluorescence) is imperative to delineate combination therapy-induced remodeling of the immune-metastatic niche in peritoneal lesions and to identify predictive biomarkers via machine learning-driven feature selection.

In conclusion, this retrospective cohort study preliminary demonstrates safety and feasibility of triple therapy in GCPM patients. While the observed TTF and OS suggest therapeutic potential, we emphasize that these findings should be interpreted within the inherent limitations of retrospective analyses. These findings provide a preliminary foundation for future prospective randomized studies. The data presented here warrant validation through prospective randomized controlled trials to establish efficacy and refine patient selection criteria, particularly focusing on individuals with

preserved functional status (ECOG performance status ≤ 1).

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CONSORT 2010 statement

The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Informed consent statement

Due to the anonymous nature and non-interventional design of this study, the Ethics Committee of Suzhou Municipal Hospital approved the waiver of informed consent requirement.

Authors' contributions

Data curation, Luyao Zhang and Xiaofeng Chen; Formal analysis, Guoqiang Wang; Funding acquisition, Ying Feng; Investigation, Luyao Zhang and Mingyang Yu; Methodology, Fen Guo, Deqiang Wang and Yueyu Fang; Project administration, Jianming Shi; Resources, Liyu Wang, Ying Feng and Xiaofeng Chen; Software, Yueyu Fang; Supervision, Xiaofeng Chen; Validation, Liyu Wang; Visualization, Yuxin Feng; Writing – original draft, Fen Guo and Deqiang Wang; Writing – review & editing, Ying Feng and Xiaofeng Chen.

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Data availability

The data used in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the relevant regulatory and independent ethics committee of the Affiliated Suzhou Hospital of Nanjing Medical University (No. KL901465) and was conducted following the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was waived as no new or invasive procedures were conducted for the study purposes and also approved by the ethics committee of the Suzhou Municipal Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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