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Safety and efficacy of systemic chemotherapy plus PD-1 inhibitor in combination with intravenous or intraperitoneal bevacizumab in gastric cancer with peritoneal metastasis

Yuxi Ma[1,2,3], Yuting Li[1,2,3], Zhenyu Lin[1,2,3], Jing Wang[1,2,3], Jianli Hu[1,2,3], Hongli Liu[1,2,3], Yali Yang[1,2,3], Junli Liu[1,2,3*] and Tao Zhang[1,2,3*]

Abstract

Background For gastric cancer patients, peritoneal metastasis poses a life-threatening risk due to the high incidence of treatment failure and disease recurrence. Conducting additional research aimed at identifying more efficacious strategies is imperative for enhancing treatment outcomes. This study examined the efficacy and safety of systemic chemotherapy plus a PD-1 inhibitor combination with intravenous or intraperitoneal bevacizumab for gastric cancer with peritoneal metastasis.

Methods We conducted the open label, two-arm pilot study involved receiving albumin-bound paclitaxel (260 mg/m^2, d1) plus S-1 (80 mg/m^2, d1-14) combined with sintilimab (200 mg, d1) and bevacizumab (7.5 mg/m^2, d1) (Arm A) intraperitoneally for moderate or large ascites or intravenously (Arm B) for non- or small ascites. The clinical trial was registered at the Chinese Clinical Trial Registry (ChiCTR2100048947 DATE: 2021-07-19).

Results Ten gastric cancer patients with peritoneal metastasis were enrolled in two arms (four in Arm A and six in Arm B) from August 19th, 2021 to June 1st, 2022. Until the end of the follow-up date, the mPFS for Arm A was 5.70 m (95% CI: 1.29–10.11), while Arm B had a mPFS of 9.07 m (95% CI: 3.79–14.35). The mOS for Arm A and Arm B was 8.43 (95% CI: 6.70-10.17) and 11.23 months (95% CI: 2.90-19.56). At least one common Grade 3/4 AE occurred in 25% of Arm A participants and 16.7% of Arm B patients.

Conclusions Albumin-bound paclitaxel plus S-1 with a PD-1 inhibitor and intraperitoneal or intravenous bevacizumab was well tolerated in gastric cancer patients with peritoneal metastasis.

*Correspondence:
Junli Liu
junli78@foxmail.com
Tao Zhang
taozhangxh@hust.edu.cn

Full list of author information is available at the end of the article

Condensed abstract
The administration of albumin-bound PTX plus S-1 with PD-1 inhibitor in conjunction with intraperitoneal or intravenous bevacizumab represents a secure and effective therapeutic approach for individuals with advanced GC featuring PM.

Keywords Gastric cancer, Peritoneal metastasis, Chemotherapy, Sintilimab, Bevacizumab

Introduction

With a grim prognosis, peritoneal metastases (PM) are detected in 30% of cases of advanced gastric cancer (GC), for which conventional treatments such as systemic chemotherapy and immunotherapy are only marginally effective [1–3]. Prior research has indicated inadequate penetration and response of systemic chemotherapy in PM as a result of the peritoneal-plasma barrier, with a median overall survival (OS) of less than 1 year and frequently considerable systemic toxicity. Hence, a therapeutic approach aimed at directly targeting the unbound cancerous cells via intraperitoneal (IP) delivery of anticancer agents may potentially serve as a viable strategy for the management of peritoneal malignancy [4].

Although conventional chemotherapy regimens for metastatic GC have been established through numerous Phase III trials, the enrollment of fewer patients with moderate or large ascites has made it challenging to develop a standard treatment for GC patients with PM. In the second-line setting, intravenous (IV) paclitaxel (PTX) has been approved as a standard of care for GC treatment. Moreover, PTX has shown promising results in gastric cancer with peritoneal metastasis (GCPM) after intravenous administration, primarily due to its high concentration in the peritoneal cavity [5]. The combination of S-1 and PTX has demonstrated a notable ability to penetrate the peritoneal cavity and has shown significant effectiveness against diffuse-type adenocarcinoma, a rapidly spreading form of cancer [5–8]. Compared to solvent-based PTX, albumin-bound nanoparticle PTX can be administered at higher doses, resulting in higher drug concentrations and fewer hypersensitive reactions in patients who have not received premedication. Studies by Shitara et al. have demonstrated that weekly nab-PTX is non-inferior to weekly solvent-based PTX in terms of OS, making it a viable regimen for second-line therapy in GC [9]. Thus, it can be inferred that the combination of S-1 and nab-PTX could potentially serve as an effective form of systemic chemotherapy for the treatment of PM because of its favorable safety profiles and efficacy outcomes.

Vascular endothelial growth factor (VEGF) may play a role in the development of malignant ascites through the role of angiogenesis and increasing the permeability of the microvasculature and the peritoneal membrane, according to recent translational research and clinical findings from limited case series [10–12]. A correlation exists between the volume of ascites and the concentration of VEGF in ascites. The level of VEGF in ascites has also been identified as a significant prognostic factor in cases of GCPM [13]. Bevacizumab, an antiangiogenic monoclonal antibody targeting VEGFA, has shown promising efficacy in combination with chemotherapy for the treatment of advanced GC in phase II studies [14]. In cases of GCPM, ascites recurrence tends to accelerate as the disease progresses. This often requires more frequent paracenteses (drainage of fluid from the abdomen) and local control measures such as intraperitoneal chemotherapy or targeted therapies. In the context of intraperitoneal administration, bevacizumab has shown promise in treating ascites associated with various solid tumors, particularly ovarian cancer [10]. In light of the efficacy of bevacizumab on malignant ascites, we implemented one arm of this trial with intraperitoneal bevacizumab for moderate or large ascites. Previous findings confirmed the significance of VEGF signaling as a crucial therapeutic target in advanced GC, with anti-angiogenic drugs like ramucirumab and apatinib demonstrating considerable efficacy [15, 16]. Taking this into account, we employed bevacizumab intravenously in GCPM with non- or small ascites as systemic therapy.

The guidelines include anti-PD-1/PD-L1 immunotherapy as a potential first or second-line treatment option due to the well-established effectiveness of immunotherapy in the management of GC [17, 18]. However, it remains unclear whether immune checkpoint inhibitors are efficacious in controlling ascites since patients with massive ascites were excluded from previous studies. A retrospective analysis has reported that nivolumab administration may improve massive ascites and offer a survival advantage in GC [19]. Therefore, incorporating a PD-1 inhibitor could be a recommended approach. Based on these findings and theoretical advancements, we designed this study to assess the safety and efficacy of intraperitoneal or intravenous administration of bevacizumab in combination with S-1 and albumin-bound PTX and the PD-1 inhibitor for advanced GCPM.

Patients and methods

Study design

The designated Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology of each participating site gave its

approval for the two cohorts trial, which was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. All participants in the study provided written informed consent prior to enrollment. The clinical trial was registered at the Chinese Clinical Trial Registry under the registration number ChiCTR2100048947.

Study population

The following key inclusion criteria were mandated in order to participate in this investigation: 18 to 75-year-old patients histologically or cytologically confirmed the presence of GC or gastroesophageal junction tumor with PM (HER2 negative). The ECOG performance status was 0–1 and the expected survival time was more than 3 months. Did not receive any therapy for GC within the last six months (chemotherapy, radiation therapy, or both). Principal exclusion criteria: The obstruction of the cardia and pylorus affected the patient's eating and gastric emptying, or had difficulty swallowing tablets. HER2-positive GC and gastroesophageal junction tumors. Subject with other malignancies, except for non-melanoma skin cancer or in-situ cervical carcinoma under adequate treatment, or other treated malignancies without evidence of recurrence for 5 years. Previously received the following therapies: anti-PD-1, anti-PD-L1 or anti-PD-L2 drugs or drugs that stimulate or co-inhibit T cell receptors (e.g., CTLA-4, OX-40, CD137). Received systemic treatment with Chinese medicines or immunomodulatory drugs (including thymosin, interferon, interleukin, except for local use to control pleural effusion) with anti-tumor indications within 2 weeks before the first administration; Active autoimmune disease requiring systemic therapy (e.g., disease-modifying drugs, glucocorticoids, or immunosuppressants) occurred within 2 years prior to first dose; Replacement therapy (such as thyroxine, insulin, or physiological glucocorticoids for adrenal or pituitary insufficiency, etc.) was not considered systemic therapy.

Treatment plan and evaluations

The study schedule is displayed in Fig. 1. Firstly, patients with PM were confirmed by previous imaging and then were conducted ultrasound examination of ascites. We determined the amount of ascites and rated them as follows: large ascites (including the entire abdominal cavity), moderate (neither large nor small), small (limited to the pelvic cavity or liver surface), or no (ascites not detected). Ascite drainage was planned prior to protocol treatment. Based on the ascites volume, we designed two cohorts

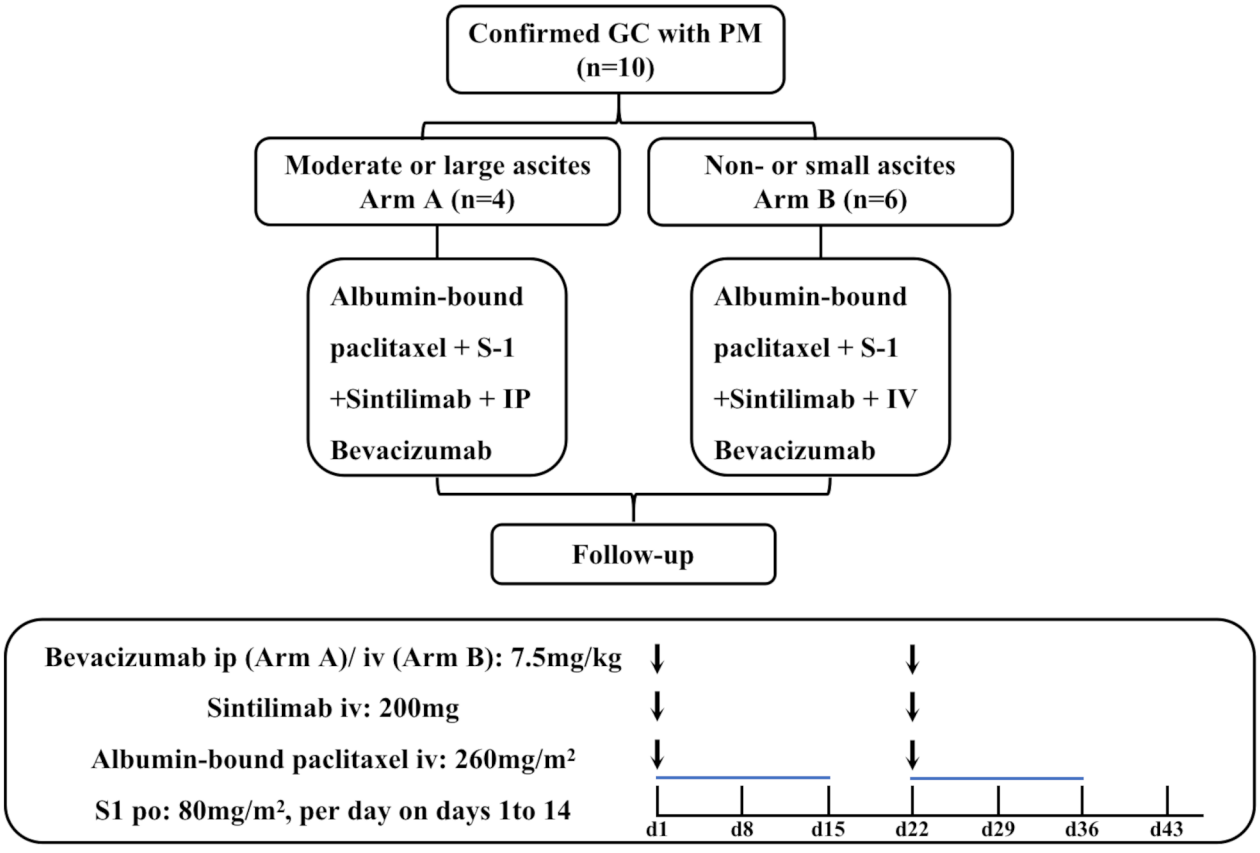


Fig. 1 Overview of study design

which were planned to receive PTX plus S-1 combined with sintilimab (albumin-bound PTX 260 mg/m^2 on days 1 plus S-1 80 mg/m^2 per day on days 1 to 14 and sintilimab 200 mg for a 3-week cycle) and bevacizumab (7.5 mg/m^2 for a 3-week cycle) (Arm A) intraperitoneally for moderate or large ascites or intravenously (Arm B) for non- or small ascites.

Dose modification

The drug dosages used were standardized in clinical settings, and any necessary modifications to the dosage were as follows when treatments were used in combination: Patients experiencing unacceptable adverse effects from one or more drugs may choose to cease this drug in question and continue with the remaining treatment regimen until disease progression or the occurrence of intolerable toxicity. Grade 3–4 non-hematological or grade 4 hematological adverse effects were all associated with a 25% reduction in the chemotherapy dosage in the subsequent cycle. Additionally, if the adverse effects persisted after the second dose reduction or if it caused a delay by more than 4 weeks, the chemotherapy regimen should be halted.

Efficacy evaluation

To assess the primary gastric tumor, we did CT or MRI screenings every two cycles in accordance with the parameters outlined in the Response Evaluation Criteria in Solid Tumors (version 1.1). The assessment of efficacy for detectable lesions was categorized into four distinct outcomes: complete response (CR), partial response (PR), stable disease (SD), and progressing disease (PD). The measurement of disease control rate (DCR) was operationalized as the ratio of patients exhibiting either CR, PR or SD. The implementation of the objective response rate (ORR) measurement entailed measuring the ratio of patients who demonstrated CR or PR. The ascites volume was assessed using CT every 2 cycles, employing a 5-point measurement approach [5]. The determination of the therapeutic efficacy of ascites, based on the evaluation standard established by the World Health Organization, was outlined as follows: CR indicated the complete disappearance of celiac effusion for a duration beyond four weeks; PR denoted a substantial drop of more than 50% in celiac effusion, which also persisted for more than four weeks; SD referred to a decrease in peritoneal effusion by less than 50% or an increase of no more than 25%; PD indicated an increase in ascites by more than 25% [20].

Table 1 Characteristics at baseline

Variables	Moderate or large ascites (Arm A: $n=4$)	Non- or small ascites (Arm B: $n=6$)
Age, median (range)[years]	49.5 (45–56)	48.5 (37–64)
Gender, female [n (%)]	2 (50%)	3 (50%)
ECOG		
0	4	6
Amount of Ascites		
Non	-	4
Small	-	2
Moderate	1	-
Large	3	-
Average ascites volume of first paracenteses	2900 ml	150 ml
Previous Interventions		
Surgery	1 (25%)	2 (33.3%)
Adjuvant Chemotherapy	1 (25%)	2 (33.3%)

End-points and statistical analysis

The primary endpoints were safety and tolerability. The Common Terminology Criteria for Adverse Events V.5.0 was used to determine the severity of each adverse event (AE). The secondary endpoint included OS, progression-free survival (PFS), DCR, and ORR. PFS and OS were calculated using the Kaplan–Meier method. Using V 26 of the IBM SPSS Statistics program, statistical analyses were conducted (SPSS Inc., Chicago, IL, USA).

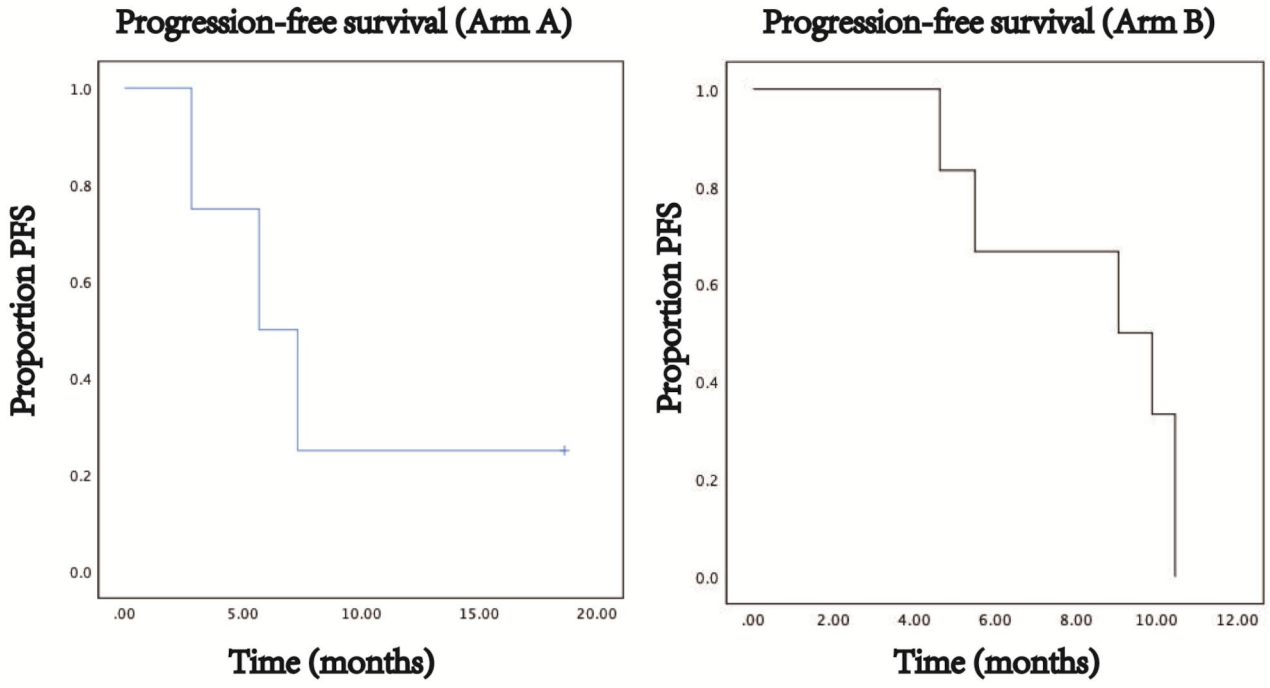
Results

Patient demographics

A total of 10 individuals were enrolled between August 2021 and June 2022 from our hospital. As listed in Table 1, the median age was 49.5 years (range, 45–56 years) in Arm A vs. 48.5 years (range, 37–64 years) in Arm B with a balanced male-to-female ratio. All of the patients had an ECOG status of 0. With an average volume of 2900 ml, all in Arm A underwent paracenteses, while one was identified as moderate ascites and three were large ascites. Two individuals in Arm B were classified as small ascites after paracenteses while the other 4 had no ascites.

Treatment outcomes between two arms

Three patients in Arm A achieved relief of ascites symptoms with 75% ORR and had a 100% DCR, who did not undergo any additional paracentesis. Among six patients in Arm B, three patients had a reduction of peritoneal and omental thickening. Up until the end of the follow-up date, the mPFS for Arm A was recorded as 5.70 months (95%CI: 1.29–10.11), whereas Arm B exhibited a mPFS of 9.07 months (95%CI: 3.79–14.35). The mOS for Arm A and Arm B was found to be 8.43 months (95%CI: 6.70-10.17) and 11.23 months (95%CI: 2.90-19.56), respectively (Figs. 2 and 3). One patient in Arm A, who initially had an ascites volume of 4500 ml, continues to exhibit effective control with PFS of 18.63 m and has not shown disease progression. Another patient in Arm B still remains alive and demonstrates an OS of 19.83 m.



Time (months)	No. at risk				PFS (95% CI)
	0	4	8	12	
Arm A	4	3	1	1	5.70 (1.29-10.11)
Arm B	6	6	4	0	9.07 (3.79-14.35)

Fig. 2 Analysis of PFS in Arm **A** and Arm **B**

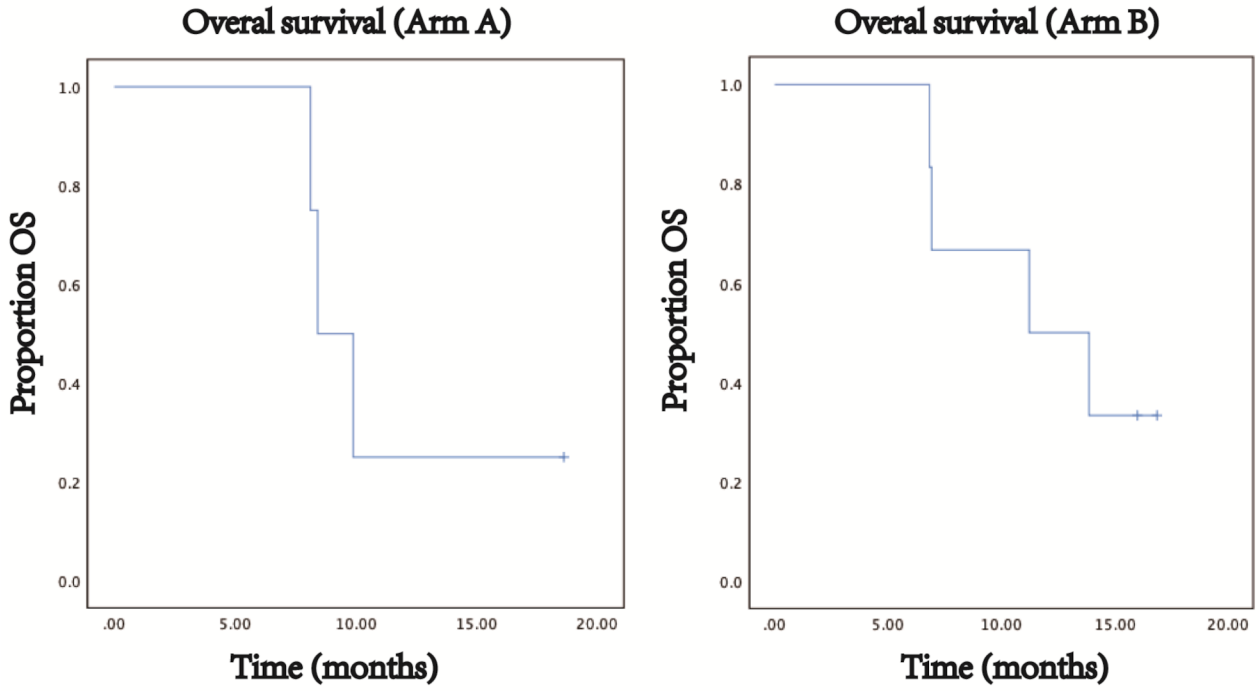
Toxicity evaluation

Both treatment arms underwent toxicity and side effect assessments, and no unforeseen severe adverse outcomes or fatalities related to treatment were observed (Table 2). The most common AE was anemia (100% in Arm A vs. 83.3% in Arm B) and all were grade 1–2. Grade 3/4 AEs happened in Arm A were hypokalemia and rash, while leukopenia, neutropenia, rash, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased in Arm B. One patient in Arm A experienced Grade 3 immune-related adverse events (irAEs), specifically presenting with a rash. No grade 5 AEs occurred.

Discussion

Metastasis to the peritoneum is a hallmark of advanced GC, a subtype characterized by poor biological behavior and an even worse prognosis [21]. Quality of life in GCPM patients is also significantly impacted by incurable malignant ascites manifested as intestinal obstruction, abdominal infection, malnourishment, and cachexia [22]. Developing innovative drug combinations will be imperative and profoundly affect this disease.

Several studies concerning the systemic chemotherapy regimen have been established for GCPM. The Japan Clinical Oncology Group (JCOG) carried out a two-arm, randomized Phase III trial (JCOG0106) merely including GCPM patients was determined that the methotrexate plus 5-fluorouracil (MF) therapy arm did not perform better than the 5-fluorouracil continuous infusion therapy arm, which proved that MF was not an appropriate choice for conventional therapy in GCPM [23]. Based on recent findings, it is now widely accepted that patients with advanced GC who have progressed on fluoropyrimidine and platinum-based combination therapy should have second-line chemotherapy with either irinotecan, docetaxel, wPTX, or ramucirumab. JCOG conducted another phase II clinical trial (JCOG0407) comparing wPTX with the 5-FU regimen as a second-line treatment for GCPM. Despite the fact that the median OS for both arms was 7.7 months, the median PFS with wPTX was longer than with 5-FU (3.7 m vs. 2.4 m) [24]. A phase II/III trial (JCOG1108/WJOG7312G) that compared FLTAX (5-fluorouracil, l-leucovorin, and paclitaxel) with 5-fluorouracil/l-leucovorin was carried out for these



Time (months)	No. at risk				OS (95% CI)
	0	5	10	15	
Arm A	4	4	1	1	8.43 (6.70-10.17)
Arm B	6	6	4	2	11.23 (2.90-19.56)

Fig. 3 Analysis of OS in Arm **A** and Arm **B**

Table 2 Toxicity evaluation (CTCAE 5.0)

Variables	Moderate or large ascites (Arm A: $n=4$)		Non- or small ascites (Arm B: $n=6$)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Leukopenia	1 (25%)	-	1 (16.7%)	1 (16.7%)
Neutropenia	2 (50%)	-	1 (16.7%)	1 (16.7%)
Anemia	4 (100%)	-	5 (83.3%)	-
Thrombocytopenia	-	-	1 (16.7%)	-
AST increased	1 (25%)	-	-	1 (16.7%)
ALT increased	2 (50%)	-	2 (33.3%)	1 (16.7%)
Hyperbilirubinemia	1 (25%)	-	4 (66.7%)	-
Hyponatremia	2 (50%)	-	1 (16.7%)	-
Hypokalemia	1 (25%)	1 (25%)	2 (33.3%)	-
Proteinuria	1 (25%)	-	-	-
Rash	-	1 (25%)	-	-

AST: aspartate aminotransferase

ALT: alanine aminotransferase

individuals with severe GCPM and showed a promising result for FLTAX. For the 5-FU/l-LV and FLTAX arms, the median OS were 6.1 and 7.3 months, respectively. mPFS was also longer in the FLTAX arm (1.9 m vs. 5.4 m) [25]. Actually, the aforementioned results reveal that systemic chemotherapy alone fails to provide adequate treatment for patients diagnosed with GCPM, necessitating the development of alternative treatment approaches.

Intraperitoneal chemotherapy demonstrates promising effects and is extensively utilized as it elevates the effective drug concentration within the cavity and diminishes plasma drug exposure along with the incidence of systemic AEs. The only randomized clinical trial on normothermic intraperitoneal chemotherapy-the PHOENIX-GC trial was reported by Ishigami et al. in 2018. However, it did not corroborate the survival advantage, with a median survival time of 17.7 months in the intraperitoneal and systemic chemotherapy group (IP) as opposed to 15.2 months in the systemic chemotherapy-only group (SP) ($p=0.08$) [26]. Recently, Kim

et al. conducted a phase I study to assess the safety and efficacy of intraperitoneal paclitaxel in combination with intravenous chemotherapy using fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in patients with GCPM. Their findings closely aligned with the results of the PHOENIX-GC study, which reported a mOS of 16.6 months and a mPFS of 9.6 months [27]. Additionally, the anticancer activity of nab-PTX following intravenous treatment was found to be comparable to that of intraperitoneal injection [28]. Alternatively, we used nab-PTX intravenously and bevacizumab intraperitoneally, which was a two-pronged approach to manage ascites.

Bevacizumab has been sanctioned by the Food and Drug Administration for the management of various malignancies, such as colorectal, non-small-cell lung, renal, and ovarian cancers [10]. However, in GC, the AVAGAST trial showed that PFS and the ORR significantly improved in individuals who were randomly assigned to receive bevacizumab with chemotherapy, but OS did not significantly improve. Investigators have recently examined the feasibility of administering bevacizumab therapy intraperitoneally for the treatment of ascites. Malignant ascites in patients with GC were the focus of a phase II, placebo-controlled, double-blind trial- AIO SUP-0108 [29]. After paracentesis, they were randomized in a 2:1 ratio to receive either a placebo or 400 mg of intraperitoneal bevacizumab. Nonetheless, the findings did not show any significant differences either in terms of paracentesis-free survival (ParFS) or the paracentesis-free period. However, it is worth noting that patients whose malignant ascites VEGF levels dropped significantly after therapy with bevacizumab showed a trend toward increased event-free survival. The use of bevacizumab intracavitary perfusion has been shown to enhance the clinical efficacy of malignant ascites treatment and optimize the quality of life in lung cancer and ovarian cancer [10]. Pascale et al. reported that the intraperitoneal and intravenous exposure ratios in systemic bevacizumab patients were markedly lower compared with systemic chemotherapy [30]. This reinforced the hypothesis for administering repeated intraperitoneal bevacizumab to achieve sufficient anti-cancer concentrations for large ascites. Yet, despite bevacizumab's dismal results in the management of ascites in GC, clinical trials are currently ongoing.

Therefore, the protocol employed in our study, involving the utilization of anti-angiogenic therapy plus immunotherapy in combination with systematic chemotherapy, has the potential to target GCPM effectively. The combination of PD-1 inhibitor and chemotherapy serves as a standard first-line treatment option for advanced GC patients with a mOS surpassing one year [17, 18]. However, the effectiveness of immune checkpoint inhibitors in managing ascites remain uncertain. In our study, Arm A enrolled the patients with moderate or large ascites, which were the extremely advanced stage of GC, coupled with the limited remaining lifespan. To achieve enhanced anti-cancer concentrations in the peritoneal cavity, intraperitoneal bevacizumab has been employed in this arm. The mPFS for Arm A was observed to be 5.70 months (95%CI: 1.29–10.11) and the mOS reached 8.43 months (95% CI: 6.70-10.17). Compared to the previous studies with malignant ascites exhibiting a low median survival time of approximately 2–3 months [31–33], our intervention yielded a noteworthy and medically relevant improvement. Arm B including patients with non- or small ascites exhibited a mPFS of 9.07 months (95%CI: 3.79–14.35), whereas mOS was 11.23 months (95% CI: 2.90-19.56), which was consistent with findings from comparable patient cohorts.

The primary objective of our study was to assess the safety and tolerability of the combined intervention. The predominant AEs observed were anemia, with a frequency of 100% in Arm A and 83.3% in Arm B. Other recorded cases of AEs were consistent with prior research and aligned with our initial hypotheses. A low frequency of grade 3 or 4 AEs showed that our treatment was safe and well tolerated in this trial.

Our investigation has several limitations. Firstly, it was conducted as a pilot study without a control group, which limited direct comparison with standard treatment. The small sample size in each study arm may introduce bias, and therefore, a randomized Phase II trial with an increased sample size is currently being planned. Additionally, detecting or quantifying PM posed challenges due to the lack of measurable lesions. The interpretation of peritoneal thickening on CT scans was subjective and could vary among interpreters. The study utilized CT imaging to assess the burden of PM and volume of ascites, following a methodology similar to the PHOENIX-GC trial.

To summarize, the administration of albumin-bound PTX plus S-1 with PD-1 inhibitor in conjunction with intraperitoneal or intravenous bevacizumab represents a secure therapeutic approach for individuals with advanced GC featuring PM.

Abbreviations

IP	Intraperiteneal
IV	Intravenous
GC	Gastric cancer
PM	Peritoneal metastases

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14206-9.

Supplementary Material 1

Supplementary Material 2

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Author contributions
TZ was granted complete access to the entirety of the data in the study, and as a result, he took the responsibility for ensuring the data's integrity and the accuracy of the data analysis. The study's concept and design were conducted by JLL and YXM. Data acquisition, analysis, and interpretation were conducted by JLL and YXM. The manuscript underwent a critical revision for significant intellectual content by LHL, YTL, ZYL, JW and JLH. YLY conducted statistical analysis.

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Data availability
The data and materials in the current study are available from the corresponding author on reasonable request.

Declarations

Human and animal rights
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

Informed consent
Informed consent was obtained from all patients for being included in the study.

Consent for publication
Not applicalble.

Competing interests
The authors declare no competing interests.

Author details
[1]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 109 Machang Road, Jianghan District, Wuhan 430022, China
[2]Hubei Key Laboratory of Precision Radiation Oncology, Wuhan 430022, China
[3]Institute of Radiation Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

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