



# Analysis of the efficacy and safety of paclitaxel (albumin-bound) combined with S-1 and oxaliplatin combined with S-1 in the first-line treatment of advanced gastric cancer: a cohort study

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**Background:** Single-drug albumin-bound paclitaxel is one of the standard second-line treatments for advanced gastric cancer. Some clinical studies suggest that albumin-bound paclitaxel combined with S-1 can be used in the first-line treatment of gastric cancer. Both the two regimens have been commonly used in the past few years. Which is more effective? What's the safety?

**Methods:** From 2016 to 2021, a total of 70 untreated patients with advanced gastric cancer were included in our study. They all received at least two cycles of chemotherapy. Among them, 37 cases received standard S-1 and oxaliplatin (SOX) regimen, and 33 cases received albumin-bound paclitaxel combined with S-1 (aTS) regimen. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events (AEs) were analyzed. The OS and PFS curves were estimated using the Kaplan-Meier method.

**Results:** The PFS of the aTS group was higher than that of the SOX group (9.27 vs. 7.03 months;  $P=0.046$ ), but there was no significant difference in the OS between the two groups (19.2 vs. 12.5 months;  $P=0.131$ ). The ORR of the aTS group was higher than that of the SOX group, and the side effects were tolerable.

**Conclusions:** Both regimens can be applied to advanced gastric cancer patients. Albumin-bound paclitaxel showed a higher ORR and could effectively prolong PFS.

**Keywords:** Albumin-bound paclitaxel; S-1; advanced gastric cancer; first-line therapy

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## Introduction

In 2020, the incidence of gastric cancer ranked sixth in the world, and it was the third leading cause of cancer-related death globally (1). In the past decade, compared with other malignancies, the progress in the treatment of gastric cancer has been relatively slow. Despite advances in the field of molecular targeted drug therapies, so far, the chemotherapy of gastric cancer has not made a breakthrough and the survival time of such patients has not been markedly improved. While the advent of immunotherapy paved the

way for some remarkable progress, at present, chemotherapy is still the cornerstone in the treatment of gastric cancer, and mainly consists of dual-drug therapy, such as oxaliplatin combined with the S-1 regimen. However, chemotherapy, as one of the main treatments, has not made any significant progress in recent years.

The guidelines from both the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) recommend oxaliplatin combined with fluorouracil as first-line therapy and

albumin-bound paclitaxel as second-line therapy in advanced gastric cancer. Efficacy of albumin-bound paclitaxel combined with S-1 in first-line treatment has recently been confirmed (2). In that study, The scheme achieves a high response rate. However, to date, there have been no studies comparing the efficacy and safety of albumin-bound paclitaxel combined with S-1 (aTS) regimen and the standard S-1 and oxaliplatin (SOX) regimen.

In recent years, our center has achieved good results when using aTS as the first-line treatment in patients with advanced gastric. This retrospective study was performed to compare the aTS regimen with standard treatment over the same period. We present the following article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-279/rc>).

## Methods

### Patients

Patients diagnosed with advanced gastric cancer and who were treated with the SOX regimen or the aTS regimen in our hospital between 2016 and 2021 were retrospectively enrolled in this study. The following inclusion criteria were applied: (I) patients >18 years old; (II) the Eastern Cooperative Oncology Group (ECOG) score was  $\leq 2$ ; (III) patients had pathologically confirmed locally advanced unresectable or metastatic gastric cancer; (IV) the tumors were human epidermal growth factor receptor 2 (HER-2) negative; (V) patients did not receive any previous radiotherapy or chemotherapy (prior adjuvant/neoadjuvant therapy was allowed if at least 6 months had elapsed between completion of adjuvant/neoadjuvant therapy); (VI) the expected survival time was >3 months; (VII) the lesions were measurable; (VIII) the functions of the liver, kidney, and bone marrow hematopoiesis were good, as indicated by absolute neutrophil count  $\geq 1,000/\text{mm}^3$ , platelet count  $\geq 7.5 \times 10^4/\text{mm}^3$ , total bilirubin  $\leq 1.5 \text{ mg/dL}$ , aspartate aminotransferase  $\leq 100 \text{ IU/L}$ , and alanine aminotransferase  $\leq 100 \text{ IU/L}$  (for patients with liver metastasis, total bilirubin  $\leq 2.0 \text{ mg/dL}$ , aspartate aminotransferase  $\leq 200 \text{ IU/L}$ , and alanine aminotransferase  $\leq 200 \text{ IU/L}$ ); and (IX) patients received at least 2 cycles of aTS or SOX treatment in our institution. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Changzhou Cancer Hospital (No. 2017-SY-012). Written informed consent was obtained from the patients for publication of this study.

### Treatment

Patients in the SOX group were administered oxaliplatin  $130 \text{ mg/m}^2$  and S-1  $40 \text{ mg/m}^2$  (b.i.d d1–14, q3w). Patients in the aTS group were given albumin-bound paclitaxel  $120 \text{ mg/m}^2$  (d1, 8) and S-1  $40 \text{ mg/m}^2$  (b.i.d d1–14, q3w). Up to 6 cycles of the treatments were administered, and if the disease remained stable after 6 cycles, oral maintenance therapy was continued with S-1. If there was disease progression or intolerable side effects, or the patients withdrew for personal reasons, the treatments were terminated.

Patients were not randomly assigned SOX or aTS treatment. A decision on which treatment regimen would be administered was made via consultation between the doctor and patient, and the following factors were considered: the patient's physical condition, economic status, treatment purpose, and the requirements for efficacy and side effects. This was deemed a better reflection of the medical situation in the real world.

### Assessments

The study was conducted to compare the efficacy and safety of the aTS regimen and the SOX regimen, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The ORR was evaluated with enhanced computed tomography (CT) every 2 cycles, including chest and abdomen CT, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (3).

Safety was assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

### Statistical analysis

The *t*-tests and chi-square tests were used to compare the baseline parameters of the patients (a two-sided 5% was considered statistically significant). The OS and PFS curves were estimated using the Kaplan-Meier method, using an unstratified log-rank test with a two-sided 5% significance level. The hazard ratio (HR) was estimated using the Cox proportional hazards model. Univariate and multivariable analyses were also performed using the Cox proportional hazards model. Univariate analysis was performed to explore prognostic factors. Statistical analyses were conducted using the SPSS 26.0 software (IBM Corp., Armonk, NY, USA).

**Table 1** Basic patient characteristics

Characteristics	aTS (n=33)	SOX (n=37)	P value
Age (years)			0.280
Median [range]	65.45 [46–78]	62.97 [36–75]	
Sex, n (%)			0.820
Male	24 (72.7)	26 (70.3)	
Female	9 (27.3)	11 (29.7)	
Disease site, n (%)			0.469
Cardia	18 (54.5)	19 (51.4)	
Gastric fundus	1 (3.0)	0 (0.0)	
Gastric body	5 (15.2)	10 (27.0)	
Gastric antrum	9 (27.3)	8 (21.6)	
Histology, n (%)			0.906
Well differentiated	0 (0.0)	0 (0.0)	
Moderately differentiated	2 (6.1)	2 (5.4)	
Poorly differentiated	31 (93.9)	35 (94.6)	
Site of metastases, n (%)			
Liver	12 (36.4)	19 (51.4)	0.208
Lung	2 (6.1)	3 (8.1)	0.740
Retroperitoneal lymph nodes	19 (57.6)	15 (40.5)	0.155
Others	13 (39.4)	20 (54.1)	0.220
Cycles of first-line chemotherapy			0.186
Mean ± standard deviation	4.81±1.42	4.49±1.75	
Cycles of posterior line chemotherapy			0.544
Mean ± standard deviation	2.1±2.19	2.04±3.15	

aTS, albumin-bound paclitaxel combined with S-1; SOX, standard S-1 and oxaliplatin.

## Results

### Basic patient characteristics

A total of 70 patients were enrolled in the study, including 37 patients in the SOX group and 33 patients in the aTS group. There were no significant differences in the baseline characteristics of the patients in the two groups (Table 1). The longest follow-up period was 2 years.

**Table 2** Efficacy of aTS and SOX treatment

Efficacy	aTS (n=33)	SOX (n=37)	P value
CR, n (%)	0 (0.0)	1 (2.7)	0.038
PR, n (%)	18 (54.5)	10 (27.0)	–
SD, n (%)	15 (45.5)	22 (59.5)	–
PD, n (%)	0 (0.0)	4 (10.8)	–
ORR (%)	54.5	29.7	–

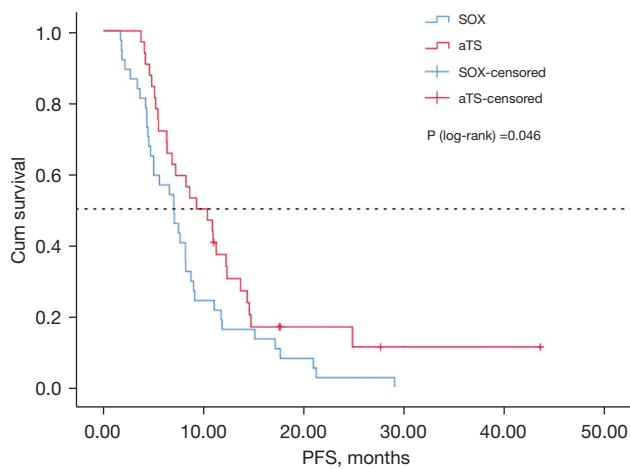
aTS, albumin-bound paclitaxel combined with S-1; SOX, standard S-1 and oxaliplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

### Efficacy and safety

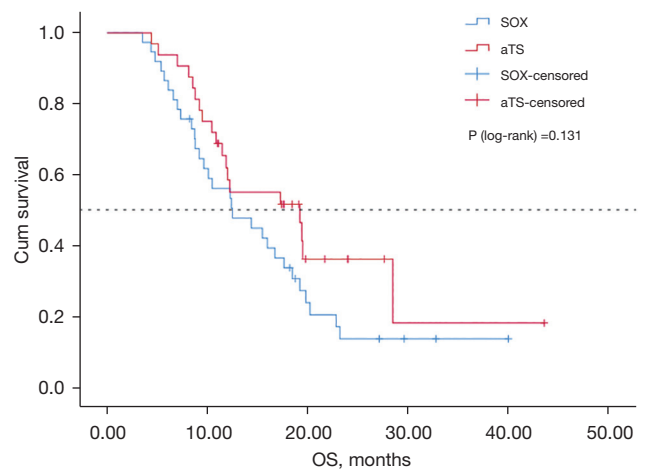
Of the 37 patients in the SOX group, 1 (2.7%) had complete response (CR), 10 (27.0%) showed partial response (PR), 22 (59.5%) had stable disease (SD), and 4 (10.8%) progressed. Of the 33 patients in the aTS group, none (0.0%) experienced CR, 18 (54.5%) showed PR, 15 (45.5%) had SD, and none (0.0%) progressed. There was a significant difference between these two groups ( $P=0.038$ ) (Table 2).

The median PFS was 7.03 months in the SOX group [95% confidence interval (CI): 4.77 to 9.29 months] and 9.27 months in the aTS group (95% CI: 5.61 to 12.91 months) ( $P=0.046$ ; Figure 1). The median OS was 12.5 months in the SOX group (95% CI: 6.83 to 18.17 months) and 19.2 months in the aTS group (95% CI: 9.48 to 28.92 months) ( $P=0.131$ ; Figure 2). Univariate analysis showed that PFS was related to chemotherapy regimen and whether there were more than 2 cycles of chemotherapy. Multivariate analysis of variance suggested that PFS was related to chemotherapy regimen (aTS vs. SOX: HR =0.605;  $P=0.047$ ; 95% CI: 0.369 to 0.992), and whether there were more than 2 cycles of chemotherapy (HR =0.228;  $P=0.000$ ; 95% CI: 0.116 to 0.452) (Table 3).

The adverse events (AEs) of all participants are summarized in Table 4. The two schemes were well-tolerated, with most side effects classified as grade 1–2 (Table 4). Neutropenia and gastrointestinal reactions were common. The incidence of peripheral neurotoxicity was high in both groups. The incidences of neutropenia and alopecia were higher in the aTS group compared to the SOX group. The incidence of thrombocytopenia in the SOX group was higher than in the aTS group, and this



**Figure 1** Kaplan-Meier PFS for aTS vs. SOX. SOX, standard S-1 and oxaliplatin; aTS, albumin-bound paclitaxel combined with S-1; PFS, progression-free survival.



**Figure 2** Kaplan-Meier OS for aTS vs. SOX. SOX, standard S-1 and oxaliplatin; aTS, albumin-bound paclitaxel combined with S-1; OS, overall survival.

**Table 3** Side effects associated with aTS and SOX treatment

Side effects	aTS (n=33)		SOX (n=37)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Diarrhea, n (%)	2 (6.1)	0 (0.0)	2 (5.4)	0 (0.0)
Nausea/vomiting, n (%)	15 (45.5)	2 (6.1)	17 (45.9)	2 (5.4)
Mucositis, n (%)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hand & foot syndrome, n (%)	3 (9.1)	0 (0.0)	3 (8.1)	1 (2.7)
Asthenia, n (%)	4 (12.1)	0 (0.0)	5 (13.5)	0 (0.0)
Live toxicity, n (%)	1 (3.0)	0 (0.0)	1 (2.7)	0 (0.0)
Renal toxicity, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy, n (%)	17 (45.5)	1 (3.0)	27 (73.0)	1 (2.7)
Neutropenia, n (%)	19 (57.6)	3 (9.1)	19 (51.3)	1 (2.7)
Thrombocytopenia, n (%)	4 (12.1)	1 (3.0)	10 (27.0)	3 (8.1)
Febrile neutropenia, n (%)	1 (3.0)	2 (6.1)	1 (2.7)	2 (5.4)
Anemia, n (%)	4 (12.1)	0 (0.0)	6 (16.2)	0 (0.0)
Alopecia, n (%)	22 (66.7)	4 (12.1)	1 (2.7)	0 (0.0)

aTS, albumin-bound paclitaxel and S-1; SOX, standard S-1 and oxaliplatin.

may be related to oxaliplatin. No obvious cardiotoxicity was observed in either group.

**Discussion**

For advanced gastric cancer, fluorouracil combined

with platinum is the most commonly used first-line treatment (4,5). The choice of platinum can be cisplatin or oxaliplatin, while fluorouracil can be either S-1 or capecitabine. Since S-1 is oral fluorouracil, it is simple and convenient to administer and is thus widely used in Asian countries, including China (6,7). The combination

**Table 4** Cox regression analysis (PFS)

Variables	Univariate Cox regression model			Multivariate Cox regression model		
	HR	95% CI	P	HR	95% CI	P
Sex (male vs. female)	0.923	0.531–1.606	0.778			
Age (years, <65 vs. ≥65)	1.106	0.679–1.803	0.685			
Disease site						
Cardia	1.0					
Gastric fundus	–	–	–			
Gastric body	1.411	0.762–2.613	0.274			
Gastric antrum	1.068	0.584–1.953	0.831			
Histology						
Differentiation (1= moderately; 2= poorly)	1.274	0.461–3.520	0.641			
Site of metastases						
Liver	0.974	0.592–1.603	0.918			
Lung	0.975	0.389–2.422	0.957			
Retroperitoneal lymph node metastasis	1.163	0.710–1.907	0.549			
Others	1.575	0.962–2.580	0.071			
Therapy (aTS vs. SOX)	0.610	0.372–0.999	0.050	0.605	0.369–0.992	0.047
Cycles of first line chemotherapy (>2 vs. 2)	0.230	0.117–0.455	0.000	0.228	0.116–0.452	0.000

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; aTS, albumin-bound paclitaxel and S-1; SOX, standard S-1 and oxaliplatin.

of docetaxel, fluorouracil, and cisplatin is the standard first-line and three-drug regimen (8), especially in Europe and the United States, and is superior to fluorouracil plus cisplatin in terms of efficiency. However, there is no statistical difference in OS compared to the conventional two-drug regimens. On the contrary, the higher incidence of toxic reactions limits its routine use. A meta-analysis found that there was no statistical difference in ORR or OS when platinum was used as a first-line treatment compared with the new generation of non-platinum drugs (paclitaxel and irinotecan). Furthermore, platinum drugs are significantly more toxic in terms of hematotoxicity, nausea, vomiting, and neurotoxicity. In the mouse model, paclitaxel and S-1 were found to have a synergistic effect (9). Several phase II or III clinical trials reported that paclitaxel or docetaxel combined with S-1 was effective and well-tolerated (10,11).

In addition, effective platinum-free first-line chemotherapy is needed, especially when patients are unable to accept platinum drugs due to renal dysfunction or other side

effects. Paclitaxel is a better choice for platinum-tolerant patients. It is therefore imperative to explore paclitaxel non-platinum chemotherapy with equivalent low toxicity as a first-line treatment.

Compared with ordinary paclitaxel, albumin-bound paclitaxel has a higher concentration in tumor tissues. Due to the change of solvent, the incidence of allergic reactions is also significantly reduced. Prophylactic antiallergic therapy is no longer needed before infusion. Presently, it is widely used in malignancies such as breast cancer, pancreatic cancer, and non-small cell lung cancer (12–14). However, in some cancer types, a study has confirmed that albumin-bound paclitaxel does not improve OS compared to common paclitaxel drugs (15). In terms of gastric cancer, current guidelines (NCCN guidelines and CSCO guidelines) recommend that albumin-bound paclitaxel can be used alone for second-line treatment of advanced gastric cancer.

A phase II trial in Japan (16) demonstrated that albumin-bound paclitaxel (NAB-PTX; 260 mg/m<sup>2</sup>, d1, q3w) as

second-line chemotherapy in advanced gastric cancer had good activity and tolerance. A phase III clinical trial (17) showed that NAB-PTX (100 mg/m<sup>2</sup>, d1, 8, and 15) once every 3–4 weeks, was as safe as solvent-based paclitaxel in terms of OS, and had fewer allergic reactions.

Recently, in the phase II clinical trial organized by Professor Xu Ruihua of Sun Yat-sen University, the efficacy and safety of albumin-bound paclitaxel combined with S-1 in the treatment of advanced gastric cancer were evaluated (2). Previously untreated patients with metastatic gastric adenocarcinoma were administered 40 mg [body surface area (BSA) <1.25 m<sup>2</sup>], 50 mg (1.25 ≤ BSA <1.50 m<sup>2</sup>), or 60 mg (BSA ≥1.50 m<sup>2</sup>) twice a day on days 1–14, combined with albumin-bound paclitaxel (120 mg/m<sup>2</sup>, d1 and 8) every 21 days. A total of 73 patients were enrolled. The median PFS was 9.63 months, and the OS rate was 14.6 months. There were 4 cases of CR and 39 cases of PR, with an ORR of 58.9% and a disease control rate (DCR) of 87.7%. Most of the toxic reactions were mild and there were no treatment-related deaths. Grade 3–4 adverse reactions occurred in 22 cases (30.1%), including leukopenia (13.7%), neutropenia (12.3%), anemia (5.5%), thrombocytopenia (1.4%), diarrhea (6.8%), etc. The study concluded that S-1 combined with albumin-bound paclitaxel is an effective and safe first-line treatment for advanced gastric cancer.

Another phase III multicenter, open-label, randomized, controlled, clinical trial protocol (18) is underway to explore the application of albumin-bound paclitaxel combined with S-1 in adjuvant chemotherapy after D2 radical resection of gastric cancer. The primary endpoint is the 3-year DFS defined as the time from randomization to the time of recurrence of the original gastric cancer, development of a new gastric cancer, or death from any cause. The secondary endpoints are OS (defined as the time from the date of randomization to the date of death from any cause) and safety (any AE).

This current retrospective study analyzed patients who were treated with SOX or aTS. The results demonstrated that the PFS of the aTS group was longer than that of the SOX group (9.27 vs. 7.03 months;  $P=0.046$ ), and the ORR was significantly increased (54.5% vs. 29.7%). Therefore, the aTS regimen may be more suitable for patients who require a reduction in tumor size over a short period of time, to relieve symptoms or to reach the maximum reducing staging to facilitate surgical options.

There was no significant difference in OS between the two groups ( $P=0.131$ ), which may be related to the second-line application of albumin-bound paclitaxel or

immunotherapy in some patients. However, the number of samples involved was small and the distribution of cases did not strictly follow the principle of randomization. Future large-scale clinical studies are warranted to verify these findings.

In summary, compared with the SOX regimen, the aTS regimen can improve the ORR and prolong the PFS, but the extension of PFS does not translate into increased OS.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Changzhou Cancer Hospital (No. 2017-SY-012). Written informed consent was obtained from the patients for publication of this study.

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