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S-1 maintenance therapy in advanced gastric cancer without disease progression after first-line chemotherapy: A retrospective analysis

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Abstract

For patients with advanced gastric cancer after chemotherapy, the optimal mode of maintenance therapy is not yet clear. This research aimed to compare the efficacy and adverse effects of S-1 maintenance therapy and follow-up observation in patients with advanced gastric cancer without disease progression after first-line combined chemotherapy. This study retrospectively analyzed 106 patients from January 2018 to December 2021. The primary endpoints were overall survival and progression-free survival, the secondary endpoint was chemotherapy-related toxicity, and the curative effects and baseline characteristics of the patients were analyzed. Longer progression-free survival and overall survival were observed in the S-1 maintenance treatment group than in the follow-up observation group ($p < 0.001$). No obvious differences existed in the subgroup results regarding progression-free survival or overall survival ($p > 0.05$). In the maintenance treatment group, the occurrence of thrombocytopenia and hand-foot syndrome was significantly increased ($p < 0.001$). No toxicity-related deaths occurred. The included patients without disease progression after first-line combined chemotherapy can achieve significant survival benefits by receiving S-1 maintenance therapy. The patient's tolerance to S-1 maintenance therapy was good.

Keywords

Gastric cancer, maintenance treatment, progression-free survival, S-1

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Introduction

The occurrence of gastric cancer (GC) has been dramatically reduced due to changes in lifestyle, control of chronic *Helicobacter pylori* infections, and early diagnosis.[1] However, GC remains the main cause of cancer-associated death worldwide, with hundreds of thousands of people dying from gastric cancer each year. At present, surgery is still the main treatment, and the average five-year survival rate is 20%–30%. Due to the lack of specificity of GC-related symptoms, more than two-thirds of patients have advanced stage or metastatic GC when confirmed diagnosis, thus losing the opportunity for surgical treatment. Notably, the recurrence and metastasis rates of GC after surgical treatment are high, and most patients will eventually die from recurrence or metastatic progression. Currently, combined chemotherapy is the basic and most effective therapy for advanced GC. Combined chemotherapy improves the 1-year survival rate and prolongs progression-free survival (PFS) compared with the best supportive symptomatic treatments.[2,3]

Fluorouracil, taxanes, and platinum are the main drugs for advanced GC. Generally, first-line chemotherapy consists of fluorouracil drugs, and platinum and/or taxane drugs are combined to form a two-drug or three-drug chemotherapy. The two-drug combination regimen of platinum and fluorouracil drugs is more commonly recommended in China.[4,5] Standard treatment for advanced GC usually lasts between four and six months, with regular follow-up after disease control has been achieved.

Maintenance treatment refers to a treatment method in which advanced malignant tumors are controlled by medication, and the original treatment plan is stopped in favor of a maintenance treatment plan until the disease progresses. Studies have suggested that maintenance treatment may be beneficial for such patients after combined chemotherapy,[6] but the optimal mode of maintenance therapy has not been clarified. S-1, a novel oral chemotherapy drug, is widely applied as a combined therapy for stages III and IV GC due to its longer half-life and superior safety profile. In this research, we reviewed cases with advanced GC who completed six to eight cycles of first-line combined chemotherapy from January 2018 to December 2021 and analyzed the clinical efficacy and adverse reactions of maintenance therapy.

Patients and methods

Patients

Up to 106 eligible patients with advanced GC from January 2018 to December 2021 were included in the present study. Patient records were deidentified and anonymized prior to analysis. All patients in this research provided informed consent.

The inclusion criteria were as follows: (1) age $\geq$ 18 years; (2) Eastern Cooperative Oncology Group Performance Status Scale[7] $\leq$ 2; (3) advanced GC with pathological diagnosis (stage IV, according to the AJCC staging system)[8]; (4) no disease progression after completion of the previous 6 to 8 cycles of combined chemotherapy, followed by observation and follow-up or S-1 maintenance; (5) radiographically measurable or evaluable disease; and (6) no other cancers. The exclusion criteria were as follows: (1) confirmed brain metastases; (2) concurrent radiotherapy; (3) disease progression after

multiple cycles of combined chemotherapy; (4) poor physical condition, which affected the prognosis due to poor basic physical condition; (5) GC not being the primary lesion but due to cancer metastasis in other tissues and organs of the body; and (6) a variety of diseases, especially the second cancer in the body except GC.

The data collected in this study included age, sex, human epidermal growth factor receptor-2, microsatellite instability status, chemotherapy-related side effects, PFS, and overall survival (OS).

Assessment of efficacy and adverse events

The tumor response of patients was evaluated via RECIST1.1[9] OS and PFS were regarded as the primary endpoints. PFS means the time from the first dose of chemotherapy to cancer progression and death (based on the first occurrence). OS was defined from the start of chemotherapy to death. The secondary endpoint was chemotherapy-related toxicities. Toxicities of chemotherapy were scaled consistently with the standard for adverse events (CTCAE) 5.0.[10]

Statistical analysis

PFS and OS were determined based on Kaplan–Meier curves. The log-rank test was applied to compare the significance in different groups. The significance of different groups was compared based on the log-rank test. We used the chi-square test and rank sum test to examine the clinical data. A Cox regression method was applied to compute hazard ratios. The significant difference was judged based on $p < 0.05$ ($p < 0.05$). SPSS software22.6 was applied for statistical analyses.

Ethics

The study was performed consistent with the Helsinki criteria. The present research was approved by the Chongqing University Cancer Hospital Committee. The patients in this study had signed written informed consent before starting the study.

Results

Patient characteristics

The patients included in this study included 61 males and 45 females; 26 patients were aged ≥ 65 years, and the Eastern Cooperative Oncology Group (ECOG) score of most patients was 0-1. Of the 106 patients, 56 received S-1 maintenance therapy (MCT group), and 50 received follow-up observation (OBS group). Table 1 summarizes the baseline characteristics (sex, age, tumor differentiation degree, ECOG score, whether the metastasis site was more than 3, HER2 status, and MSI status) of the cases. All the included cases had advanced gastric cancer confirmed by histology. There were no obvious differences in age, sex, cancer differentiation, ECOG score, metastasis site greater than 3, or HER2 or MSI status between the MCT and OBS groups ($p > 0.05$, Table 1).

Table 1. Data from all patients.

	MTC	OBS	*p*
Age			0.432
Age≥65	12	14	
Age＜65	44	36	
Gender			0.761
Male	33	28	
Female	23	22	
ECOG PS score			0.585
0-1	53	46	
2	3	4	
Tumor differentiation			0.324
Well	11	6	
Moderately	18	17	
Poorly	22	20	
Signet ring cell	5	7	
Metastatic sites			0.647
> 3	30	29	
≤ 3	26	21	
HER2			0.854
−	31	30	
+	12	7	
++	8	7	
+++	5	6	
MSI			0.325
MSS	53	47	
MSI-H	3	3	

MSI: microsatellite instability; MTC: maintenance treatment; OBS: observation; ECOG PS: Eastern Cooperative Oncology Group Performance Status Scale; HER2: human epidermal growth factor receptor-2; MSI-H: microsatellite instability-high; MSS: microsatellite stable.

Survival analysis

As of December 2021, 102 patients (96.2%) had reached the endpoint. The median PFS (mPFS) of the MTC and OBS groups was 11.500 months (95% CI, 10.961–12.039) and 8.300 months (95% CI, 8.011–8.589), respectively. Compared to the observation group, the PFS of the maintenance treatment group had a good trend ($p < 0.001$, Figure 1). At the last follow-up, 6.6% ($n = 7$) of cases were alive (four in the MTC group; and three in the OBS group). The median OS was 19.100 months (95% CI, 18.818–19.382) in the MTC group and 16.300 months (15.759–16.841) in the OBS group. Prolongation of OS was observed in the MTC group compared to the OBS group ($p < 0.001$, Figure 2).

Differences in OS and PFS of the two groups were checked within the prognostic variables, such as sex, age, tumor differentiation, ECOG score, whether the metastasis site was greater than 3, and HER2 and MSI status. No obvious differences existed in subgroup results regarding these two variables ($p > 0.05$) (Table 2).

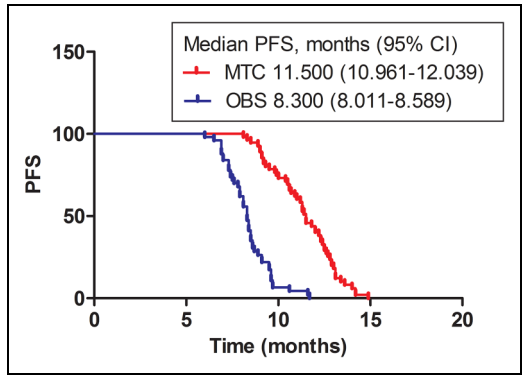

Figure 1. Kaplan–Meier curve of PFS for all cases ($p > 0.05$). In the MTC group, 56 patients received S-1 maintenance therapy; in the OBS group, 50 patients received follow-up observation.
PFS: progression-free survival; MTC: maintenance treatment; OBS: observation.

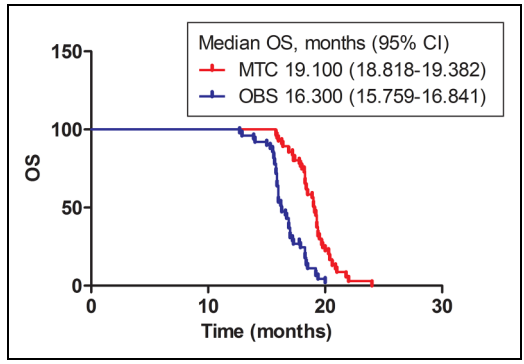

Figure 2. K–M curve of OS for all cases ($p > 0.05$). In the MTC group, 56 patients received S-1 maintenance therapy; in the OBS group, 50 patients received follow-up observation.
K–M: Kaplan–Meier; MTC: maintenance treatment; OBS: observation; OS: overall survival.

Adverse events

Compared with that in the OBS group, the occurrence of HFS and thrombocytopenia in the MCT group was obviously increased ($p < 0.05$). Chemotherapy-related toxicities are presented in Table 3. Most of the adverse reactions were effectively controlled and alleviated by symptomatic treatment or a reduction in the S-1 dose. No toxicity-related deaths were reported. All patients received 6 to 8 cycles of combination chemotherapy. Seven of the 56 patients in the MCT group received S-1 reduction (three due to severe thrombocytopenia and four due to severe hand-foot syndrome (HFS)), and two patients discontinued MCT therapy due to the progression of their disease. These patients included in the analysis received at least four cycles of MCT.

Table 2. Multivariate Cox results of variables impacting PFS and OS.

	No. of patients	PFS			OS		
		HR	95% CI	*p*	HR	95% CI	*p*
Age		1.252	0.764–2.054	0.373	0.911	0.551–1.505	0.715
≥65	26						
<65	80						
Gender		1.034	0.668–1.601	0.881	0.932	0.603–1.439	0.751
Female	45						
Male	61						
ECOG		0.564	0.242–1.315	0.185	1.770	0.748–4.186	0.194
0-1	99						
2	7						
Tumor differentiation		1.143	0.739–1.770	0.548	1.247	0.817–1.902	0.307
Well/moderately	52						
Poorly/signet ring cell	54						
Number of metastatic sites		1.058	0.695–1.610	0.793	1.319	0.865–2.013	0.199
>3	59						
≤3	47						
HER2		0.893	0.584–1.365	0.600	0.955	0.626–1.454	0.828
−	61						
+	45						
MSI		0.637	0.250–1.628	0.347	0.923	0.385–2.214	0.858
MSS	100						
MSI-H	6						

HR: hazard ratio; MSI: microsatellite instability; HER2: human epidermal growth factor receptor-2; MSI-H: microsatellite instability-high; MSS: microsatellite stable; ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival; OS: overall survival.

Discussion

S-1, an oral anticancer agent derived from fluorouracil, consists of tegafur and two modulators: oteracil and gemcitabine. S-1 has the following advantages compared with 5-FU: ① it has a higher blood concentration and stronger anticancer activity; ② it has an obvious reduction in drug toxicity; and ③ it is more convenient for drug administration. In stage II trials, the effective rate of the drug was ~ 40% in recurrent GC.[11,12]

S-1-based regimens had significant clinically relevant advantages over 5-FU-based regimens according to the incidence of toxicity-related death, febrile neutropenia, and grade 3-4 stomatitis.[13] The meta-analysis results indicated that S-1 can replace 5-FU in this field due to the greater survival benefit of S-1.[14,15] S-1 also exhibits a promising toxicity profile and a lower incidence of HFS than capecitabine. After the administration of a SOX chemotherapy regimen following D2 gastrectomy, the patients in the experimental group received S-1 monotherapy for 6 months. Fewer patients relapsed in the experimental group during the first 5 years postoperatively than in the control group. According to the comparison results, the 5-year relapse-free survival (RFS) of the experimental group was obviously improved ($p = 0.047$; HR, 0.662; 95% CI, 0.441–0.994). The 5-year OS

Table 3. Toxicities.

	MTC				OBS				*p*
	Grade				Grade				
Event	1	2	3	4	1	2	3	4	
Neutropenia	10	4	2	0	6	3	3	0	0.688
Thrombocytopenia	14	10	3	0	5	3	0	0	<0.001
Anemia	10	5	2	0	10	4	2	0	0.883
Nausea/vomiting	10	5	2	0	8	5	1	0	0.791
Diarrhea	4	2	0	0	5	2	0	0	0.617
Nephrotoxicity	5	2	0	0	4	3	0	0	0.792
Hepatic toxicity	6	3	0	0	5	1	0	0	0.520
Stomatitis	7	2	0	0	5	0	0	0	0.332
HFS	12	9	3	1	3	0	0	0	<0.001
Paresthesia	6	3	0	0	4	0	0	0	0.186

MTC: maintenance treatment; OBS: observation; HFS: hand-foot syndrome

was obviously higher in the experimental group after surgery than in the other group ($p = 0.042$; HR, 0.634). Meanwhile, except for HFS, the chemotherapy-related toxicities reported in the experimental group were comparable to those in other groups.[16]

In a variety of advanced solid tumors, combined chemotherapy remains one of the main treatments, and first-line chemotherapy mostly progresses to tumor progression or unacceptable toxic reactions. Prolonged chemotherapy usually increases the cumulative toxicity of chemotherapy while prolonging PFS. Therefore, the concepts of degraded treatment and maintenance treatment have been described for several solid tumors. The maintenance treatment aim is to maintain the tumor regression achieved by combined chemotherapy while avoiding the increase in cumulative toxicity due to prolonged chemotherapy. The concept of maintenance therapy was established in different solid tumors, such as GC and colorectal cancer.[17,18] In a phase III controlled, prospective clinical study of gastric cancer maintenance treatment, sequential capecitabine monotherapy after four cycles of paclitaxel combined with capecitabine failed to prolong the overall survival compared with cisplatin combined with capecitabine for six cycles but measurably improved the treatment-related adverse reactions and quality of life.[19] The results of the Mateo trial showed that S-1 maintenance after 3 months of platinum-based combination chemotherapy, compared with continuous *p* combination chemotherapy, PFS and OS were comparable, and the number of AEs related to S-1 maintenance was reduced.[20] In other GCr maintenance studies, patients who did not progress after first-line chemotherapies, including cisplatin, docetaxel, and XELOX, were randomized to capecitabine maintenance treatment. These studies showed obviously better median PFS and median OS in patients receiving maintenance therapy than in those not receiving maintenance therapy, and the occurrence of grade 3/4 AEs and hematological toxicities was infrequent during maintenance therapy.[21,22] The first-line chemotherapy scheme for such patients is based on platinum, fluorouracil, and/or taxanes combined to form a two-drug or three-drug

chemotherapy scheme. Follow-up was performed regularly after control was obtained, and there were no standardized protocols for subsequent maintenance therapy.

In the present research, we reviewed cases with advanced GC who completed 6 to 8 cycles of palliative combined chemotherapy from January 2018 to December 2021. The mPFS of MTC patients treated with S-1 maintenance therapy was 11.500 months, which was obviously longer than that of the OBS group under follow-up observation. Meanwhile, the median OS of MTC cases was also longer than that of OBS cases. Differences in PFS and OS of the MTC and OBS groups were also analyzed within the layers of potential prognostic variables, such as sex, age, tumor differentiation, ECOG score, whether the site of metastasis was greater than 3, and HER2 and MSI status. There were no obvious differences in the subgroup analyses for PFS or OS. In terms of chemotherapy-related toxicities and reactions, the incidence of HFS and thrombocytopenia was obviously increased in the MCT group ($p < 0.05$). Most of the adverse reactions were effectively relieved and controlled by symptomatic treatment and reduction of the S-1 dose, and the patient's tolerance to S-1 maintenance therapy was good. No toxicokinetic-related deaths were observed. Chemotherapy-related toxicities were also observed in the OBS group, which may be related to the combination chemotherapy previously given to patients in this group. Currently, there exists no standard therapy for cases with advanced GC, and the efficacy of the latter-line therapy is poor. After first-line combined chemotherapy, when the patient's tumor reached PR or SD, S-1 maintenance therapy could prolong PFS and OS.

This retrospective research had several limitations, including the research nature, small sample number, and heterogeneity of treatment. Nevertheless, the study data reflect the real-world results of maintenance therapy and follow-up observation. We believe that this study provides a new basis for S-1 maintenance therapy in this field.

Conclusion

This study found that S-1 maintenance was well tolerated and prolonged PFS and OS in patients with advanced GC after first-line combined chemotherapy tumor control. However, it is necessary to further verify the conclusion by large sample prospective research.

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Authors' contributions

Conception and design: Ting Wang, Luchun Li. Administrative support: Ting Wang, Luchun Li. Provision of study materials: Yan Li, Shuangyi Lei. Collection and assembly of data: Zhijuan Wu, Huiwen Ma. Data analysis: Lulu Wang. All authors wrote and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This research was approved by the present Hospital (no. 2018jcyjA3710; Approval date: September 2018).

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