Original Article

The efficacy and toxicity of adjuvant S-1 schedule with 2-week administration followed by 1-week rest in gastric cancer patients

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Background: This study aimed to investigate the clinical outcome of adjuvant S-1 with 2-week administration followed by a 1-week rest for locally advanced gastric cancer (GC) patients.

Methods: The current study was a single retrospective cohort study that focused on the efficacy and toxicity of adjuvant S-1 with a 3-week schedule. A total of 60 patients who underwent total or subtotal gastrectomy plus D2 lymph node dissection and adjuvant S-1 treatment were identified. S-1 treatment began within 4 weeks after the operation; it was administered orally for 2 weeks, followed by a 1-week rest. The dose of S-1 was adjusted depending on adverse events (AEs), with at least 80 mg administered daily. The completion of 1-year S-1 was defined as S-1 continuation for 1 year with over 70% of the planned dose. Patients were followed up with for 5 years postoperatively and underwent hematologic tests and assessments of clinical symptoms every 3–6 weeks for 1 year after surgery. Computed tomography of the abdomen and panendoscopy were performed every 6 months during the first 2 years and at 1-year intervals thereafter until year 5 after surgery.

Results: The completion rate of 1-year adjuvant S-1 was 71.7%, and the 3-year disease-free survival and overall survival rates were 70.2% and 79.5%, respectively. Seventeen patients did not complete S-1 for 1 year, including 11 patients with tumor recurrence and 6 patients who developed intolerance. Most AEs of S-1 were grade 1–2, and the most frequent AEs (>20%) included anemia, fatigue, pigmentation, nausea, and diarrhea. The most common grade 3–4 AE was fatigue, which was observed in 6.7% of patients. Most patients tolerated the side effects.

Conclusions: The results of our study confirm that the efficacy and safety of schedule modification of adjuvant S-1 treatment in patients with GC who underwent gastrectomy with D2 lymph node dissection are equal to those in a previous phase 3 study.

Keywords: S-1; gastric cancer (GC); adjuvant; gastrectomy

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Introduction

Gastric cancer (GC) is one of the most common cancers worldwide and is the seventh leading cause of cancer-related death in Taiwan (1). The gold standard treatment for operable disease is gastrectomy with extended lymph node dissection, followed by adjuvant chemotherapy or chemoradiotherapy for selected patients. A previous study, the MAGIC trial, proved the role of adjuvant chemotherapy; however, this study was conducted in Western countries, and the procedure for lymph node dissection was different from that used in Eastern countries, such as Japan and Korea (2). Recently, several studies have proven the role of adjuvant chemotherapy and have shown that adjuvant chemotherapy improves the overall survival (OS) in stage II/III patients with GC (3-6). However, despite adjuvant chemotherapy for 6 months or 1 year, some patients experienced intolerance to adverse events (AEs) or tumor recurrence.

S-1 is a fourth-generation oral form of fluoropyrimidine and consists of the 5-fluorouracil prodrug tegafur with two modulators, oteracil and gimeracil (7). The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) study was designed to evaluate the role of S-1 in patients with GC who underwent gastrectomy plus D2 lymph node dissection, particularly for East Asian patients. The results of this study demonstrated that the OS rate in the adjuvant S-1 group was higher than that in the surgery alone group. The most common reasons for lack of adherence to adjuvant S-1 chemotherapy in the ACTS-GC study included refusal of the patient because of AEs, a decision by the investigators because of AEs or complications, disease recurrence or distant metastasis, the presence of a second primary malignancy, and transfer to another hospital (5). There were other reasons reported, such as immediate use after surgery, initial overdose of S-1, stage I cancer, and creatinine clearance <66 mL/min (8,9). However, even if the percentage of grade 3–4 AEs was low, 13.7% and 42.4% of patients with GC withdrew due to intolerance or required dose reduction, respectively, contributing to a 1-year S-1 completion rate of 65.8%. For patients who completed S-1 for 1 year, the dose reduction rate was still high at up to 46.5%. Furthermore, 1-year S-1 completion has been reported to be associated with improved OS (5,6). Therefore, it is very important to increase compliance and lower the AEs of S-1; in order to reach this goal, schedule modification or dose adjustment are very common in clinical practice.

Dose adjustment of S-1 is an important issue for patients with GC. Sakuramoto *et al.* revealed that patients who received more than 70% of the planned dose intensity were found to have a greater survival outcome than those who did not (10). Miyatani *et al.* reported that a lower dose of S-1 was an independent prognostic factor of lower OS in multivariate analysis for patients with stage II/III GC (11). Conversely, growing evidence has shown that modifying the treatment schedule could increase the 1-year completion rate for adjuvant S-1 therapy in stage II or III patients with GC (12-14). A Japanese study showed that the 1-year S-1 completion rate was as high as 89% for a schedule of 2-week administration followed by a 1-week rest, although the number of enrolled patients was relatively small (13). Iwasa *et al.* reported that 40% of GC patients received treatment schedule modification, and the duration of the planned 1-year period of S-1 treatment was found in 73% of the patients (12). According to the ACTG-GC trial, a survival benefit has been found in patients with 1-year completion of S-1 compared to those who did not complete a full year of treatment. Two Japanese studies also demonstrated that OS and relapse-free survival were improved in patients who completed 12 months of adjuvant therapy with S-1 compared to those who did not (8,9). In addition, a phase 3 OPAS-1 study showed that when using S-1 as adjuvant chemotherapy, a 1-year duration is significantly more effective than a 6-month duration for stage 2 GC patients (15). This finding also confirmed the importance of 1-year S-1 treatment. Therefore, schedule modification may decrease drug intolerance, increase compliance, and improve the 1-year completion rate of S-1, contributing to greater survival outcomes. However, to the best of our knowledge, only a limited number of studies have focused on the outcome of schedule modification of adjuvant S-1 treatment (12,13,16).

The present study is a retrospective cohort study, and aimed to investigate the clinical outcome of adjuvant S-1 with schedule modification in stage II/III patients with GC who underwent gastrectomy plus D2 lymph node dissection, including drug tolerability, 1-year S-1 completion rate, survival data, and occurrence of AEs.

We present the study in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-477).

Methods

Patient selection

A cohort of 1,163 patients with GC who were treated at

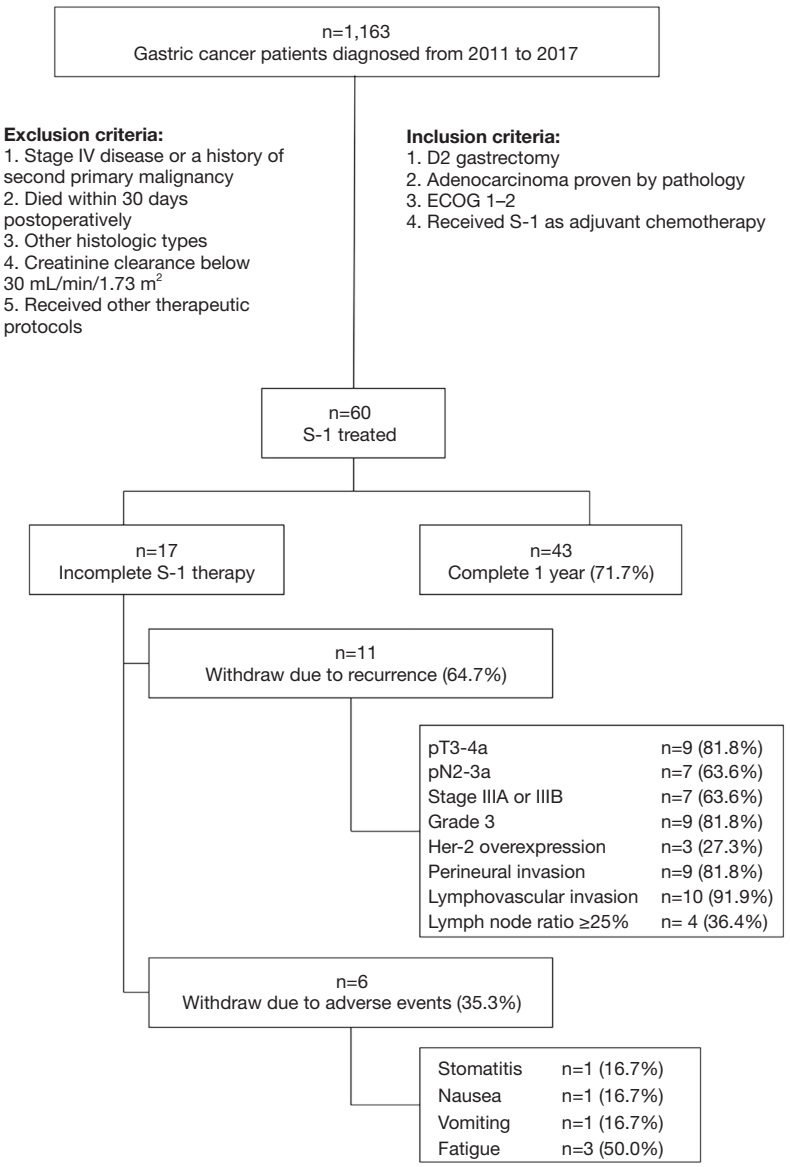

Figure 1 Flowchart for identifying gastric cancer patients who received gastrectomy and D2 lymph node dissection treated with S-1 as adjuvant chemotherapy. ECOG, Eastern Cooperative Oncology Group.

Kaohsiung Chang Gung Memorial Hospital from January 2011 to December 2017 were retrospectively reviewed. The inclusion criteria included (I) patients with GC who underwent total or subtotal gastrectomy with D2 lymph node dissection; (II) gastric adenocarcinoma proved by pathology; (III) Eastern Cooperative Oncology Group (ECOG) 1–2; and (IV) patients who received S-1 alone for adjuvant treatment. The exclusion criteria were (I) patients with stage IV disease or a history of second primary malignancy; (II) patients who died within 30 days postoperatively; (III) other histologic types, such as neuroendocrine tumor, gastrointestinal stromal tumor, or small cell carcinoma; (IV) creatinine clearance <30 mL/min/1.73 m^2; and (V) any patient who underwent other therapeutic protocols, such as adjuvant combination chemotherapy, adjuvant radiotherapy, or concurrent chemoradiotherapy, and supportive care. Finally, only 60 patients who met the inclusion/exclusion criteria were identified. The algorithm used is shown in *Figure 1*.

Each patient with GC in our study underwent abdominal computed tomography (CT) to determine the clinical stage

based on the 7th edition of the American Joint Committee on Cancer (AJCC) staging system (17,18). In addition, according to the study design of the ACTS-GC trial, patients defined as stage III by the AJCC 7th edition were excluded if their stage was revised to stage IV by the AJCC 6th edition (5,6,19). The status of Her-2 was assessed by immunohistochemistry. Low expression of Her-2 (0 or 1+) was defined as negative, and Her-2 (3+) was regarded as overexpression; the equivocal for Her-2 overexpression (2+) was referred for fluorescence *in situ* hybridization analysis (20). The lymph node ratio is defined as the number of positive metastatic nodes divided by the total number of dissected nodes (21).

Study design and S-1 treatment

The current study was a single-institute retrospective cohort study which aimed to investigate the efficacy and toxicity of adjuvant S-1 with 2-week administration followed by a 1-week rest for locally advanced GC patients. S-1 was administered as adjuvant chemotherapy for patients with GC who underwent gastrectomy with D2 lymph node dissection (5,6), and was administered within 4 weeks after surgery. S-1 was administered orally for 2 weeks, followed by a 1-week rest. The dose of S-1 was administered based on body surface area (BSA): BSA <1.25 m^2, 40 mg twice daily; 1.25 to <1.5 m^2, 50 mg twice daily; ≥1.5 m^2, 60 mg twice daily. The dosage was adjusted depending on AEs, with at least 80 mg administered daily. This 3-week cycle was repeated during the first year after surgery, except in the event of intolerance or tumor recurrence. The completion of 1-year S-1 was defined as S-1 continuation for 1 year with over 70% planned dose (22).

The symptoms and signs were assessed and documented based on the Common Terminology Criteria for Adverse Events version 4.0 before the initiation of each cycle (2,23). Safety issues were documented for a toxicity assessment, and the dose was modified according to the toxicity profile. In principle, if a patient had a hematologic toxicity of grades 3 or 4, or a nonhematological toxicity of grades 2–4, their daily dose was reduced from 120 to 100 mg or 100 to 80 mg. The definition of intolerance indicated an inability to tolerate the AEs of S-1 for GC patients.

Patients were followed up with for 5 years postoperatively. Patients visited the outpatient clinic for S-1 and underwent hematologic tests and assessments of clinical symptoms every 3–6 weeks for 1 year after surgery. Abdominal CT was performed every 3–6 months after surgery and panendoscopy was performed every 6 months during the first 2 years and at 1-year intervals thereafter until year 5 after surgery. Disease recurrence was determined based on the results of the abdominal CT or panendoscopy.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). The chi-square test was used to assess the differences between groups for categorical variables, and the statistical difference between the ACTS-GC trial and the current study. Kaplan-Meier curves were used to estimate disease-free survival (DFS) and OS.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201900004B0) and written informed consent from the patients or their families was not considered necessary because of the retrospective design of this study.

Results

Patient characteristics

Upon retrospective review of our GC database, 60 patients with GC who underwent gastrectomy with D2 lymph node dissection followed by S-1 as adjuvant chemotherapy were identified. The sample included 30 male patients and 30 female patients with a median age of 64 years (range, 35–87 years). The median BSA was 1.62 m^2 (1.21–2.06 m^2). Moreover, 8 (13.3%), 34 (56.7%), and 18 (30.0%) patients were diagnosed with pathologic T2, T3, and T4a status, respectively, whereas 20 (33.3%), 14 (23.3%), 17 (28.3%), and 9 (15.0%) had pathologic N0, N1, N2, and N3a statuses, respectively. The tumor stage showed that 15 (25.0%), 16 (26.7%), 17 (28.3%), and 12 patients (20.0%) were stage IIA, IIB, IIIA, and IIIB, respectively. Tumor grade analyses showed that 2 (3.3%), 17 (28.3%), and 41 patients (68.3%) had grade 1, 2, and 3, respectively. Five patients experienced Her-2 overexpression (8.3%) and 11 patients (18.3%) had a lymph node ratio ≥25%; there were 39 patients (65.0%) with perineural invasion and 46 patients (76.6%) with lymphovascular invasion. At the time of analysis, the median follow-up period was 37.5 months for all 60 patients. The clinicopathological characteristics of the patients with GC

Table 1 Characteristics of 60 patients with gastric adenocarcinoma who underwent surgical resection receiving S-1 as adjuvant chemotherapy

Characteristics	Value
Age (years), median [range]	64 [35–87]
Sex, n (%)	
Male	30 (50.0)
Female	30 (50.0)
ECOG performance status, n (%)	
1	51 (85.0)
2	9 (15.0)
Body surface area (m^2), median (range)	1.62 (1.21–2.06)
pT status, n (%)	
2	8 (13.3)
3	34 (56.7)
4a	18 (30.0)
pN status, n (%)	
0	20 (33.3)
1	14 (23.3)
2	17 (28.3)
3a	9 (15.0)
Pathologic tumor stage, n (%)	
IIA	15 (25.0)
IIB	16 (26.7)
IIIA	17 (28.3)
IIIB	12 (20.0)
Grade, n (%)	
1	2 (3.3)
2	17 (28.3)
3	41 (68.3)
Her-2 overexpression, n (%)	
Yes	5 (8.3)
No	55 (91.7)
Perineural invasion, n (%)	
Yes	39 (65.0)
No	21 (35.0)
Lymphovascular invasion, n (%)	
Yes	46 (76.6)
No	14 (23.3)
Lymph node ratio, n (%)	
≥25%	11 (18.3)
<25%	49 (81.7)

ECOG, Eastern Cooperative Oncology Group.

are shown in *Table 1*.

Analysis of S-1 administration

The median 3-year DFS and OS rates were 70.2% and 79.5%, respectively (*Figure 2*). The initial dose of S-1 was administered according to BSA: BSA <1.25 m^2, 40 mg twice daily; 1.25 to <1.5 m^2, 50 mg twice daily; ≥1.5 m^2, 60 mg twice daily. Thirteen patients (21.7%) had a dose reduction, and the median dose was 50 mg twice daily. Among the 60 patients with GC receiving S-1 as adjuvant chemotherapy, the completion rate of 1-year adjuvant S-1 was 71.7%. Seventeen patients did not complete S-1 for 1 year, including 11 patients with tumor recurrence, and six patients who developed intolerance to AEs. The 11 patients with tumor recurrence had a higher percentage of pT3-4a, pN2-3a, stage IIIA or IIIB, grade 3, Her-2 overexpression, perineural invasion, lymphovascular invasion, and lymph node ratio ≥25%. Six patients were intolerant to S-1, including stomatitis in 1 patient, nausea in 1 patient, vomiting in 1 patient, and fatigue in 3 patients. The results of S-1 administration are shown in *Figure 1*.

In addition, we excluded 11 patients who received S-1 as adjuvant chemotherapy with disease recurrence; subsequently, a total of 49 patients were identified, including 43 patients who completed 1-year S-1 and the other six patients without 1-year S-1 due to intolerance to AEs. The patients who completed 1-year S-1 were found to have superior 3-year DFS (91.8% *vs.* 50.0%, P=0.009, *Figure 3A*) and 3-year OS (90.7% *vs.* 66.7%, P=0.010, *Figure 3B*) compared to those who did not complete a full year of treatment.

Adverse events

S-1 administration included hematological and non-hematological AEs, and any grade >20% was found in anemia, nausea, diarrhea, fatigue, and pigmentation. Most AEs were grades 1–2, and grade 3–4 toxicities were very rare, including leukopenia (1.6%), anemia (1.6%), diarrhea (1.6%), stomatitis (1.6%), nausea (3.3%), vomiting (1.6%), and fatigue (6.7%). Most patients tolerated the side effects of S-1, and only six patients withdrew due to serious toxicity. No patients experienced treatment-related deaths. The results of these AEs are shown in *Figure 4*.

Discussion

The gold standard treatment for operable GC is

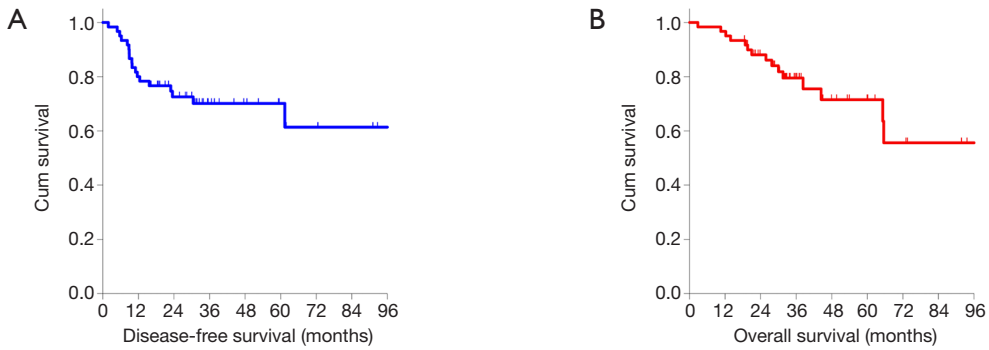

Figure 2 Kaplan-Meier curves of 3-year disease-free survival (DFS) and overall survival (OS) rates in gastric cancer patients receiving adjuvant S-1 treatment. (A) DFS; (B) OS.

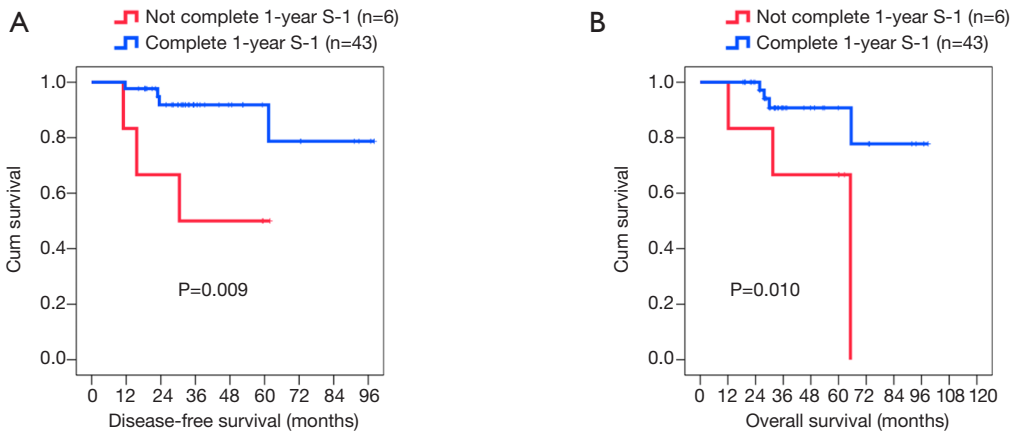

Figure 3 Kaplan-Meier curves comparing disease-free survival (DFS) and overall survival (OS) between gastric cancer patients with or without completion of adjuvant S-1 for 1 year. (A) DFS; (B) OS.

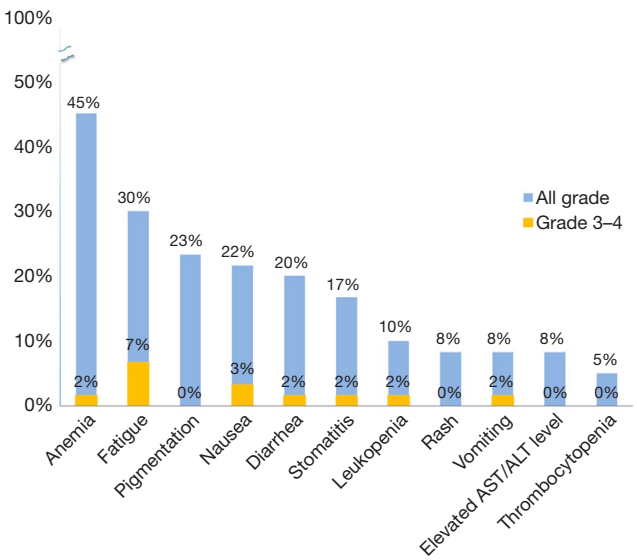

Figure 4 Adverse events of S-1 administration in 60 patients with gastric adenocarcinoma.

gastrectomy with lymph node dissection for operable patients with GC. In East Asian countries, most surgeons perform D2 lymphadenectomy for operable patients with GC; this practice seems to be sufficient for stage I patients with GC, and adjuvant treatment is not necessary. Moreover, based on the extensive surgical procedure, the necessity of adjuvant treatment with aggressive intravenous chemotherapy or radiotherapy for patients with locally advanced cancer is still of concern. Recently, some studies have shown that S-1 is an effective adjuvant chemotherapy for stage II and III patients with GC who underwent gastrectomy with D2 lymph node dissection in East Asia (5,6). Therefore, S-1 has become a suitable and tolerable adjuvant chemotherapy for patients with locally advanced GC who underwent surgical resection in Taiwan.

Although S-1 is an oral form of chemotherapy, the 1-year completion rate is not very high. The ACTS-GC trial showed that the compliance of 1-year S-1 completion

Table 2 Comparison of the current study and previous study

Variables	ACTS-GC trial (n=517)	Current study (n=60)	P value
Schedule of S-1	4-week on/2-week off	2-week on/1-week off	
1-year S-1 completion rate	65.8%	71.7%	0.36
3-year DFS rate	72.2%	70.2%	0.73
3-year OS rate	80.1%	79.5%	0.99
S-1 discontinuation rate due to AEs	27.7%	10.0%	0.003*
AEs			
Leukopenia	59.4%	10.0%	<0.001*
Anemia	90.1%	45.0%	<0.001*
Thrombocytopenia	25.9%	5.0%	<0.001*
Diarrhea	59.8%	20.0%	<0.001*
Nausea	39.1%	21.6%	0.008*
Vomiting	22.6%	8.3%	0.010*
Stomatitis	32.1%	16.7%	0.014*
Skin rash	32.5%	8.3%	<0.001*
Elevated AST/ALT	44.9%	8.3%	<0.001*
Fatigue	59.0%	30.0%	<0.001*
Pigmentation	46.6%	23.3%	0.001*

*, statistically significant. DFS, disease-free survival; OS, overall survival; AE, adverse event; ACTS-GC, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer; AST, aspartate transaminase ALT, alanine aminotransferase.

is only 65.8%, and the patients with non-continuation experienced tumor recurrence or intolerance to AEs (5,6). This finding was also reported by other real-world adjuvant S-1 studies, with similar completion rates for 1-year S-1 ranging from 59% to 69%, including studies from Japan, Korea, and Hong Kong (24-26). Moreover, the dose reduction rate is another issue. In the ACTS-GC trial, 42.4% of patients with GC had adjuvant S-1 treatment with dose reduction; in addition, the dose reduction rate was high at up to 73.3% of all patients with GC in a Hong Kong study and 31% of patients with GC who completed 1-year S-1 treatment (5,24,26). In contrast, a Japanese study showed that there was a significantly higher 1-year completion rate and a lower percentage of grade 3–4 AEs for stage II or III patients with GC who were administered S-1 as adjuvant treatment for 2 weeks, followed by a 1-week rest, compared to those with S-1 administration for 4 weeks, followed by a 2-week rest (13). Most importantly, several studies have confirmed that the DFS and OS in patients with GC who completed 1-year S-1 treatment were higher than those in patients with non-continuation of 1-year S-1 treatment (5,6,9,24). Therefore, initial schedule modification of S-1 to increase the 1-year S-1 completion rate and decrease AEs may be reasonable for clinical practice. In addition, our study also showed that the 3-year DFS and OS rates were equal and the AEs of S-1 administration were lower compared to those in a previous phase 3 study (*Table 2*). Therefore, schedule modification with 2-week administration followed by a 1-week rest may have greater tolerance of S-1, lower AEs, and similar survival outcomes, indicating that the protocol of S-1 administration in our study is feasible and should be considered for clinical practice.

Histologic type is a well-known prognostic factor for patients with GC, and several studies have shown that poorly differentiated GC is associated with a more advanced stage and more negative prognosis compared with those for well-differentiated GC (27-29). In addition, the percentage of P21 and P53 loss in poorly differentiated GC was higher, contributing to more aggressive disease and poorer clinical

outcome (29). In addition, several studies have reported that lymph node ratio was an independent prognostic factor regardless of the number of lymph node metastases (30-32). In our study, patients with tumor recurrence were found to have a higher percentage of grade 3 and lymph node ratio ≥25%. Thus, for these patients with poorly differentiated histology or high lymph node ratio, oral S-1 alone may be inadequate, and combination chemotherapy rather than a single chemotherapy regimen should be considered, but this issue needs more clinical data for verification.

In the analysis of side effects, most AEs of S-1 administration were grade 1 or 2, and our study had fewer grade 3–4 AEs. Only six patients withdrew from adjuvant S-1 treatment due to intolerance to side effects, accounting for only 10.0%, which was lower than the 27.7% observed in the ACTS-GC trial (5). Compared with those in previous studies, the percentage and severity of AEs were lower in our study, suggesting that schedule modification may be safer and more comfortable for patients with GC, especially if they only received total or subtotal gastrectomy and extended lymph node dissection.

This study has several limitations. First, the study was retrospectively designed, and all patients were treated at a single institution; hence, the sample size was relatively small. Second, the median follow-up period was not long enough, resulting in no obvious difference in survival analysis for some parameters. However, to the best of our knowledge, the present study constitutes the largest series to investigate the clinical outcome of adjuvant S-1 with schedule modification and may thus be useful for clinical practice for patients with GC.

Conclusions

The results of our study confirm that the efficacy and safety of schedule modification of adjuvant S-1 treatment in patients with GC who underwent gastrectomy with D2 lymph node dissection are equal to those in a previous phase 3 study. Further larger prospective studies to clarify the effect of this treatment protocol are warranted.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-477). The authors have no conflicts of interest to declare.

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). The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201900004B0) and written informed consent from the patients or their families was not considered necessary because of the retrospective design of this study.

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