Original article

Title: Comparison of Two-week and Four-week S-1 administration as adjuvant chemotherapy for advanced gastric cancer

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Abstract

Background: A 4-week administration of tegafur/gimeracil/oteracil (S-1) followed by a 2-week rest is the standard adjuvant chemotherapy for surgically resected advanced gastric cancer. This study aimed to evaluate the oncological feasibility of a 2-week S-1 administration followed by a 1-week rest, which is frequently applied in clinical practice to reduce toxicity and improve drug adherence.

Methods: We retrospectively enrolled patients with stage II/III gastric cancer who received S-1 adjuvant chemotherapy following radical gastrectomy from 2006 to 2016 in three institutions. Two-week and 4-week regimen cohorts were compared for relative dose intensity (RDI) as a primary outcome, and treatment completion rate, adverse event incidence, overall survival (OS), and relapse-free survival (RFS) as secondary outcomes. Confounders were adjusted for using propensity score matching (PSM).

Results: One hundred thirty-four patients received the 2-week regimen and 121 patients received the 4-week regimen. Ninety-five patients were extracted from each group after PSM. The RDIs of S-1 in the 2-week and 4-week cohorts were 73.5% and 69.9%, respectively (p=0.35), which were not significantly different. The treatment completion rate (54.7% vs. 53.7%, p=1.0), incidence of grade ≥3 adverse events (7.4% vs. 12.6%,

p=0.33), 3-year OS (76.4% vs. 82.7%, *p*=0.78), and 3-year RFS (71.3% vs. 73.4%, *p*=0.70) did not significantly differ between both cohorts.

Conclusions: The 2-week S-1 adjuvant chemotherapy could not improve drug adherence in terms of RDI, but its relapse rates were not significantly different compared with those of the 4-week regimen. The 2-week regimen might be considered as an option depending on the patient's status.

Keywords: gastric cancer, S-1, adjuvant chemotherapy, 2-week administration, propensity-score matched analysis

Introduction

Adjuvant chemotherapy with tegafur/gimeracil/oteracil (S-1) has become the standard therapy for pathological stage II or III gastric cancer in Japan since the results of the ACTS-GC trial [1,2]. This standard regimen consists of a 4-week administration of S-1 (80–120 mg/day orally) followed by a 2-week rest as one course (4-week regimen), which is continued for 1 year in a total of eight courses. In the phase III clinical trial, postoperative S-1 administration showed a 10% higher 3-year survival rate and 12.6% higher 3-year recurrence-free survival rate than those achieved in surgery alone.

However, the standard 4-week regimen has an insufficient completion rate, at 50–73% [1,3–7]. Recently, the JCOG1104 trial demonstrated that adjuvant chemotherapy with S-1 administered for 6 months was significantly inferior in terms of relapse-free survival (RFS) and overall survival (OS) than S-1 administered for 1 year in patients with stage II gastric cancer [8]. Thus, the completion rate of adjuvant chemotherapy is quite important to improve survival time even in patients with stage II cancer. To reduce adverse effects and improve drug adherence, modified S-1 administration schedules have been widely applied in clinical practice [9,10]. Among

these, a 2-week S-1 administration followed by a 1-week rest (2-week regimen) was reported to reduce toxicity and improve drug adherence while maintaining the same dose of S-1 as the standard 4-week regimen [10,11]. In a previous multicenter randomized trial, the 2-week regimen showed a higher treatment completion rate and fewer adverse events (AE) than the 4-week regimen [12]. However, this trial had a fairly small sample size and short-term observation period. Therefore, the long-term oncological feasibility of the 2-week regimen remains unclear. Moreover, the relative dose intensity (RDI) of the 2-week regimen was slightly higher than that of the 4-week regimen in the trial. This modified regimen might show equal or better oncological outcomes compared with the standard 4-week regimen.

This multicenter retrospective cohort study aimed to evaluate the hypothesis that the 2-week S-1 adjuvant chemotherapy following radical gastrectomy is less toxic and has higher RDI than the 4-week regimen.

Methods

Cohort development

One university hospital (University of Tsukuba Hospital) and two district hospitals (Southern-Tohoku General Hospital and Tsukuba Medical Center Hospital) participated in this study. We enrolled consecutive patients who underwent S-1 adjuvant chemotherapy following curative gastrectomy between January 2007 and December 2016. The patients had histologically confirmed gastric adenocarcinoma, diagnosed as pathological stage II or III (excluding T1 or T3N0, based on the Union for International Cancer Control [UICC] TNM classification, 8th edition). The exclusion criteria were as follows: carcinoma in the gastric stump (following gastrectomy), presence of a synchronous primary malignant disease, and history of preoperative chemotherapy or chemoradiotherapy. The protocol was approved by the institutional review board of each participating institution, and the study was conducted in accordance with the Declaration of Helsinki and national guidelines.

Treatment

Physicians basically prescribe S-1 as adjuvant chemotherapy according to the Japanese Gastric Cancer Association (JGCA) guidelines, 4th edition [2], in the participating institutions, although the choice between the 2-week or 4-week regimen is based on preference. In this study, we divided patients into two groups; the 2-week group started S-1 for 2 weeks followed by 1 week of rest (2-week regimen) and the 4-week group started S-1 for 4 weeks followed by 2 weeks of rest (4-week regimen). These schedules were repeated for 1 year until tumor recurrence, unacceptable toxicity, or refusal by the patient to undergo further treatment. Dosages of 80–120 mg/day were administered according to the patient's body surface area. The reference dose was allowed to decrease based on creatinine clearance. The dose reduction or change from the 4-week to the 2-week regimen was carried out at the physician's discretion according to the patients' toxicity profiles. AE were assessed using the common toxicity criteria of the National Cancer Institute (version 4.0) which was translated by JCOG (CTCAE v4.0 - JCOG). In the anemia category, patients who had already reached grade 1 at baseline were reevaluated by subtracting 1 from the original grade (one grade lower) according to JCOG criteria. Dose intensity (DI) was calculated as the ratio of the

total dose per square meter of body surface area, divided by the total treatment duration. RDI was calculated by dividing the received DI by the projected DI.

Propensity score matching

The two cohorts showed a significant difference in patient background due to bias in the selection of S-1 regimen among the participating institutions (Supplementary Table 1). Therefore, we adjusted for potential confounding factors between the two groups using propensity score matching (PSM). Covariates included those factors affecting the selection between the 2-week and 4-week regimens, i.e., age, sex, preoperative Eastern Cooperative Oncology Group performance status (ECOG-PS), renal function, surgical procedure, postoperative complications, and pathological stage. The propensity score was estimated using a logistic regression model and greedy matching (ratio 1:1, without replacement) with a caliper width equal to 0.03 of the standard deviation of the logit of the estimated propensity score.

Outcomes and statistical analysis

After matching and fixing the parameters of enrolled cases, investigators collected all outcome data. The main outcome was RDI. Secondary outcomes included treatment completion rate, incidence of dose reduction and schedule change, AE, OS, and RFS. OS and RFS were assessed using the Kaplan-Meier method and log‐rank test. Hazard ratios (HRs) were estimated using the stratified Cox model. Continuous variables were compared using *t*-tests, and categorical variables using Fisher's exact test. All statistical tests were two-sided, and *p*-values of ≤0.05 were considered to indicate statistical significance. All analyses were performed with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Stage classification and evaluation of resected specimens were performed in accordance with the 4th edition of the JGCA guidelines [2]. Although this study was retrospective, we estimated the sample size required to verify our hypothesis. We considered that there was clinical significance if the RDI in the 2-week regimen was 10% higher than that in the 4-week regimen. Assuming a one-sided alpha level of 0.05 and a statistical power of 80%, we estimated the sample size for each group to be 95.

Results

Patient characteristics

We enrolled 255 patients, 83 of whom were from the University of Tsukuba Hospital, 154 from Southern-Tohoku General Hospital, and 18 from Tsukuba Medical Center Hospital. One hundred thirty-four patients started with the 2-week regimen of S-1 as adjuvant chemotherapy, and 121 patients started with the 4-week regimen. The 2-week regimen tended to be selected at the University of Tsukuba Hospital and Tsukuba Medical Center Hospital, and the 4-week regimen at the Southern-Tohoku General Hospital (Supplementary Table 1). After PSM, 95 patients were extracted from each group for final analyses. Table 1 shows the patient and tumor characteristics pre- and post-PSM. After PSM, no significant differences in confounding factors were found between the two groups. However, the timing of starting adjuvant chemotherapy was significantly later in the 2-week group.

Treatment adherence and adverse events

The RDIs of administered S-1 were 73.5% and 69.9% in the 2-week and 4-week groups, respectively (Table 2), which were not significantly different (p=0.35).

The treatment completion rates for S-1 were 91.6% and 90.5% at 3 months, 77.9% and 81.1% at 6 months, and 54.7% and 53.7% at 1 year after initiation of S-1 treatment for the 2-week and 4-week regimens, respectively. The frequency of dose reduction was similar in both groups. Schedule change from the 4-week to the 2-week regimen was observed in 24.2% of patients. Table 3 summarizes the AE in each treatment group. The incidence of AE of all grades was 82.1% in the 2-week group and 96.8% in the 4-week group ($p<0.01$). The incidence of grade 3 AE was 7.4% in the 2-week group and 12.6% in the 4-week group, showing no significant difference ($p=0.33$). No grade 4 or 5 AE were observed in both groups.

Oncological outcomes

The median observation period after surgery was 53.3 months in the 2-week group and 53.8 months in the 4-week group. Fig.1 shows the survival curves obtained using the Kaplan-Meier method. The 3-year OS and RFS rates were 76.4% (95% confidence interval [CI] 65.8–84.2) and 71.3% (95% CI 60.7–71.5) in the 2-week group, and 82.7% (95% CI 72.8–89.2) and 73.4% (95% CI 62.9–81.4) in the 4-week group, respectively. The HRs for overall mortality and recurrence mortality in the 2-

week group compared with the 4-week group were 1.08 (95% CI 0.63–1.85, p=0.78) and 0.91 (95% CI 0.57–1.45, p=0.70), respectively. Although the Kaplan-Meier curves showed that the line of 2-week group went under the line of 4-week group, there was no significant difference between the two groups. Tumor recurrence after adjuvant chemotherapy was observed in 24 cases (25.3%) in the 2-week group and 29 cases (30.5%) in the 4-week group (Table 4). Peritoneum-only recurrence and hematogenous-only were frequently observed in both groups.

Discussion

In this study, we hypothesized that the 2-week regimen of S-1 shows a higher RDI and less toxicity than the standard 4-week regimen as adjuvant chemotherapy for advanced gastric cancer following gastrectomy. However, we observed no significant difference in RDI between both regimens, and the severe toxicity was similar in both groups. We also found no difference in 3-year OS and RFS. Therefore, the 2-week regimen did not show any obvious clinical benefit in this study.

Some researchers have applied modified schedules of S-1 adjuvant chemotherapy after curative gastric cancer resection to improve RDI or reduce toxicity. The 2-week S-1 regimen can be administered with the same dose as the standard 4-week regimen and is often used as a schedule change from the 4-week regimen in the clinical setting. Additionally, in patients with difficulty tolerating the standard normal doses of S-1, the 2-week regimen is often selected from the start of adjuvant chemotherapy according to the discretion of the attending physician. The 2-week S-1 regimen was first reported as treatment for unresectable or recurrent gastric cancer [10]. In that retrospective study, the incidence of overall AE was 77% in the 2-week regimen and 93% in the 4-week regimen. The treatment completion rate for S-1 at 6 months was

85% in the 2-week regimen and 40% in the 4-week regimen. For the adjuvant setting, a randomized scheduling study with a 2-week S-1 regimen was conducted in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [13]. These findings showed that the 2-week S-1 regimen improved the treatment completion rate and reduced the AE compared with the 4-week regimen. In our study, although the 2-week group had many patients with poor ECOG-PS, we adjusted the confounders for patient background using PSM.

RDI is the ratio of the delivered DI of chemotherapeutic agents to the standard referential DI. Maintaining a higher RDI has been shown to improve clinical outcomes in various cancers [14,15]. Also in gastric cancer, RDI has been reported as an important prognostic factor in patients receiving S-1 adjuvant chemotherapy [5,16]. Miyatani et al. reported an optimal RDI cutoff value for S-1 adjuvant chemotherapy [16]. They divided patients into two groups by a cutoff value of 64.5% using receiver operating characteristic curve analysis, and the high-RDI group showed better 5-year OS and RFS. In the randomized trial mentioned above, the RDI for the 2-week regimen was 83.8%, which was significantly higher than 70.0% for the 4-week regimen [12], so we conducted this present multicenter study with the prospect of

adding 10% to the RDI in the 2-week regimen. However, our study resulted in an RDI of 73.5% in the 2-week group and 69.9% in the 4-week group, with no significant difference. This finding could be partly explained by the low completion rate of S-1 in the 2-week group. In the randomized trial, the completion rate at 12 months of the 2-week regimen was 89%, which was higher than the 54.7% in our study. Meanwhile, the completion rates of the 4-week regimen were 49% in that previous report and 53.7% in our study, which were equivalent. The lower completion rate in our study may be attributed to the inclusion patients from two district hospitals, which might have no strict dose reduction protocols, reflecting real clinical practice. Another reason was the difference in research design. The previous study was a prospective randomized controlled trial, whereas our study was a retrospective cohort study. The choice between the 2-week and 4-week regimens was at the discretion of the attending physician in view of the actual patient, and the basis for their judgment was unclear. In this study, the incidence of AE of all grades was low in the 2-week group as expected; however, it did not improve the RDI and completion rate. These results might indicate potential vulnerabilities in the 2-week group patients that were not adjusted with our PSM analysis. We selected confounders that were considered to affect the selection of

adjuvant treatment schedules, such as age, preoperative PS, postoperative complications, pathological stage, and renal function, in PSM. Those confounders were well matched; however, patients who were considered difficult to tolerate standard dose adjuvant chemotherapy remained more in the 2-week group than 4-week group. Therefore, other confounders that might affect to drug adherence, such as postoperative oral intake, or PS after the surgery, should be included in PSM.

While several reports have shown that S-1 schedule modification is superior to the standard regimen in terms of RDI, treatment completion rate, and incidence of AE, there have been no reports that this regimen has improved long-term outcomes [3,9–12,17]. In this study, OS and RFS as well as recurrence rate and recurrence pattern were not significantly different between the two groups. Although this study did not focus on the non-inferiority of the 2-week regimen, the long-term outcomes of this modified regimen seemed comparable to those of the standard 4-week regimen. Therefore, this regimen is an acceptable option for patients who are considered to have difficulty tolerating the standard regimen. On the other hand, the RDI or completion rate of the 2-week regimen in this study was insufficient, and we should also focus on the development of supportive therapies to control toxicity from S-1 treatment.

Our study has some limitations. First, there was bias in S-1 regimen selection due to the participating institutions, which was not adjustable (Supplementary Table 1). We developed this cohort included three hospitals in which physicians could prescribe both regimen at first, however, as a result, the decision of regimen choice was a biased distribution by participated hospitals; the 2-week regimen was preferred in two hospitals and the 4-week regimen was common in the other hospital. Regimen selection and dose reduction criteria at each institution were ambiguous, therefore the results may differ from those of prospective randomized controlled trials performed with strict protocols. Second, the actual doses of S-1 that the patients received might have been different, because we only retrospectively collected prescription data. Finally, residual confounders might have been present, which we have not investigated, such as pre- and postoperative changes in nutritional status, cognitive function, mental status, and family support. Nevertheless, the results of this study are thought to reflect the real-world setting and are clinically valuable.

In conclusion, the 2-week S-1 regimen showed a similar RDI, incidence of severe AE, and oncological outcomes as the 4-week regimen. Although the standard

adjuvant chemotherapy after gastrectomy is the 4-week regimen, the 2-week regimen is an option that can be used depending on the patient's status.

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This study was approved by T-CReDO (Tsukuba Clinical Research & Development Organization) (H29-320).

5 Ethics declarations

Conflict of interest

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

Tables

Table 1. Patients' Characteristics and Operating Findings Before and After Propensity score matching (PSM)

Table 1. Patients' Characteristics and Operating Findings Before and After Propensity score matching (PSM)

		Pre-PSM			Post-PSM		
		2-week group	4-week group	*p* value	2-week group	4-week group	*p* value
No. (%)		(n=134)	(n=121)		(n=95)	(n=95)	
Age	Median	69.0	65.5	0.14	67.0	66.0	0.55
Sex	Male	97 (72.4)	91 (75.2)	0.53	67 (70.5)	72 (75.8)	0.41
	Female	37 (27.6)	29 (24.8)		28 (29.6)	23 (24.2)	
BMI	Median	22.6	22.9	0.99	22.7	22.8	0.79
ECOG-PS	0	126 (94.0)	121 (100)	0.006	95 (100)	95 (100)	1.0
	1-2	8 (6.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Renal dysfunction	Ccr<60	45 (33.6)	40 (33.1)	1.0	28 (29.5)	26 (24.4)	0.75
Liver dysfunction		4 (3.0)	4 (3.3)	1.0	3 (3.2)	3 (3.2)	1.0
Cardiac dysfunction		4 (3.0)	9 (7.4)	0.15	4 (4.2)	6 (6.3)	0.75
Pulmonary dysfunction		2 (1.5)	3 (2.5)	0.67	1 (1.1)	2 (2.1)	1.0
Surgical procedure	TG	70 (52.2)	64 (5.9)	0.92	46 (48.4)	48 (50.5)	0.77
	Other	64 (47.8)	57 (47.1)		49 (51.6)	47 (49.5)	
Postoperative complication		20 (14.9)	36 (29.8)	0.0043	19 (20)	19 (20)	1.0
Postoperative hospitalization	Median (days)	11.0	14.0	0.003	11.0	12.0	0.11
Postoperative weight loss	Median (%)	10.2	9.9	0.52	9.8	9.6	0.67

pStage	II	56 (41.8)	41 (33.9)	0.19	41 (43.2)	38 (40)	0.66
	III	78 (58.2)	80 (66.1)		54 (56.8)	57 (60)	
Histological type	Undifferentiated	95 (70.9)	79 (65.3)	0.34	67 (70.5)	67 (70.5)	1.0
	Differentiated	39 (29.1)	42 (34.7)		28 (29.5)	28 (29.5)	
Postoperative period before starting S-1	Median (weeks)	6.6	5.4	0.0004	6.4	5.4	0.0052

ECOG-PS; Eastern Cooperative Oncology Group Performance Status, Ccr; creatinine clearance, TG; total gastrectomy, Other; distal gastrectomy, proximal gastrectomy, pylorus-preserving gastrectomy, Postoperative complication: ≥grade 2 (Clavien-Dindo classification) , pStage; pathological stage

Table 2. Adherence / feasibility of each treatment group

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Variables		2-week group (n=95)	4-week group (n=95)	*p* value
RDI (%)	mean±SD	73.5±31.2	69.9±30.7	0.35
	Median (IQR)	87.5 (50.3, 100)	76.0 (46.9, 100)	
Completion rate (%)				
3 months		91.6	90.5	
6 months		77.9	81.1	
9 months		69.5	69.5	
12 months		54.7	53.7	1.0
Dose down or Schedule change rates (%)		58.9	66.3	0.37
Dose down (%)		58.9	57.9	
Schedule change (%)			24.2	

RDI; relative dose intensity

Table 3. Adverse events in each treatment group

Adverse events (%)	2-week group (n=95)					4-week group (n=95)				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3
Overall					7 (7.4)					12 (12.6)
Leukopenia	14 (14.7)	5 (5.3)	0 (0)	0 (0)	0 (0)	13 (13.7)	10 (10.5)	1 (1.1)	0 (0)	1 (1.1)
Neutropenia	18 (18.9)	7 (7.4)	0 (0)	0 (0)	0 (0)	35 (36.8)	24 (25.3)	3 (3.2)	0 (0)	3 (3.2)
Thrombocytopenia	4 (4.2)	1 (1.1)	0 (0)	0 (0)	0 (0)	12 (12.6)	2 (2.1)	0 (0)	0 (0)	0 (0)
Anemia	13 (13.7)	2 (2.1)	0 (0)	0 (0)	0 (0)	17 (17.9)	1 (1.1)	1 (1.1)	0 (0)	1 (1.1)
Elevated AST level	7 (7.4)	2 (2.1)	0 (0)	0 (0)	0 (0)	11 (11.6)	1 (1.1)	3 (3.2)	0 (0)	3 (3.2)
Elevated ALT level	6 (6.3)	0 (0)	2 (2.1)	0 (0)	2 (2.1)	11 (11.6)	3 (3.2)	0 (0)	0 (0)	0 (0)
Elevated total bilirubin level	11 (11.6)	2 (2.1)	0 (0)	0 (0)	0 (0)	9 (9.5)	2 (2.1)	1 (1.1)	0 (0)	1 (1.1)
Oral mucositis	7 (7.4)	3 (3.2)	0 (0)	0 (0)	0 (0)	6 (6.3)	4 (4.2)	1 (1.1)	0 (0)	1 (1.1)
Anorexia	14 (14.7)	10 (10.5)	2 (2.1)	0 (0)	2 (2.1)	16 (8.4)	14 (14.7)	3 (3.2)	0 (0)	3 (3.2)
Nausea	8 (8.4)	4 (4.2)	0 (0)	0 (0)	0 (0)	9 (9.5)	11 (11.6)	1 (1.1)	0 (0)	1 (1.1)
Vomiting	3 (3.2)	1 (1.1)	1 (1.1)	0 (0)	1 (1.1)	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)
Fatigue	6 (6.3)	10 (10.5)	1 (1.1)	0 (0)	1 (1.1)	3 (3.2)	7 (7.4)	0 (0)	0 (0)	0 (0)
Diarrhea	14 (14.7)	8 (8.4)	0 (0)	0 (0)	0 (0)	9 (9.5)	12 (12.6)	3 (3.2)	0 (0)	3 (3.2)
Others	9 (9.5)	1 (1.1)	1* (1.1)	0 (0)	1* (1.1)	13 (13.7)	4 (4.2)	0 (0)	0 (0)	0 (0)

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Grades of adverse events were defined according to the Common Toxicity Criteria of the National Cancer Institute (version 4.0)

AST, aspartate aminotransferase, ALT, alanine aminotransferase

Table 3. Adverse events in each treatment group

Table 4. Oncologic outcomes

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No. (%)		2-week group (n=95)	4-week group (n=95)	*p* value
Recurrence		24 (25.3)	29 (30.5)	0.42
	Peritoneum	12	12	
	Hematogenous	7	11	
	Lymph nodes	4	6	
	Local	1	0	
Mortality		27 (28.4)	26 (27.4)	0.87
	Death of recurrence	18	18	
	Death of others	9	8	

Figure captionss

Fig. 1

Kaplan-Meier curves for overall survival (A) and relapse-free survival (B). The 3-year overall survival was 76.4% in the 2-week group and 82.7% in the 4-week group. The 3-year relaps-free survival was 71.3% in the 2-week group and 73.4% in the 4-week group. There was no significant difference beween two groups.

Fig.1 Kaplan-Meier curves for overall survival (A) and relapse-free survival (B).