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<< COMMENT 1 >>

Abstract. Methods, please briefly describe measures of efficacy and safety outcomes and how patients were followed up. Importantly, the study design should be clearly indicated here. Results, please provide specific data for the safety outcomes.

- ANSWER: Thanks for your comments. According to your suggestions, we have added the description about the measures of efficacy and safety outcomes and how patients were followed up. In addition, we also added the description of the study designed and the specific data for the safety outcome. These descriptions were all added in the abstract section. Please evaluate it.

Abstract/*Methods and Results*

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 ……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 five years postoperatively and underwent hematologic tests and assessments of clinical symptoms every 3–6 weeks for one year after surgery. Computed tomography of the abdomen and panendoscopy were performed every six months during the first two 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%.....Most adverse events (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 adverse event was fatigue, which was observed in 6.7% of patients. Most patients tolerated the side effects.

- CHANGE: Abstract/*Methods and Results***, page 3, line 5**
Abstract/*Methods and Results***, page 3, line 11**
Abstract/*Methods and Results***, page 4, line 21**

<< COMMENT 2 >>
The conclusion should be made with cautions because there was no a control group. Evidence from single-arm study is low for clinical implications.

- ANSWER: Thanks for your comments. According to your suggestion, we have revised the conclusion to avoid over-interpretation in our manuscript. Please evaluate it.

Abstract/*Conclusions*

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. (**delete**: it may be reasonable and feasible for clinical practice for these patients)

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. (**delete**: it may be reasonable and feasible for clinical practice for these patients) Further larger prospective studies to clarify the effect of this treatment protocol are warranted.

- CHANGE: Abstract/*Conclusions***, page 4, line 28**
Conclusions, page 20, line 292

<< COMMENT 3 >>

Introduction. It would be helpful to review reasons for lack of adherence to adjunct S-1 chemotherapy. In this part, the other important point is whether the efficacy is maintained or decreased after schedule modification or dose adjustment. The authors should talk some on this.

- ANSWER: Thanks for your comments. According to your suggestion, we have added the review of reasons for lack of adherence to adjuvant S-1 treatment. In addition, we also added the description of dose adjustment and schedule modification based on previous published studies. Please evaluate it.

Introduction/*second and third paragraph*

S-1 is a fourth-generation oral form of fluoropyrimidine …..The most common reasons for lack of adherence to adjuvant S-1 chemotherapy in the ACTS-GS 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…..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 overall survival 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….. 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-GS 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 overall survival 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……

References

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11. Miyatani K, Saito H, Shimizu S, Kono Y, Murakami Y, Shishido Y, et al. Late start and insufficient S-1 dose in adjuvant chemotherapy can lead to poor prognosis in stage II/III gastric cancer. Int J Clin Oncol. 2019;24(10):1190-6.

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15. Yoshikawa T, Terashima M, Mizusawa J, Nunobe S, Nishida Y, Yamada T, et al. Four courses versus eight courses of adjuvant S-1 for patients with stage II gastric cancer (JCOG1104 [OPAS-1]): an open-label, phase 3, non-inferiority, randomised trial. Lancet Gastroenterol Hepatol. 2019;4(3):208-16.

- CHANGE: Introduction/*second paragraph*, **page 6, line 55**

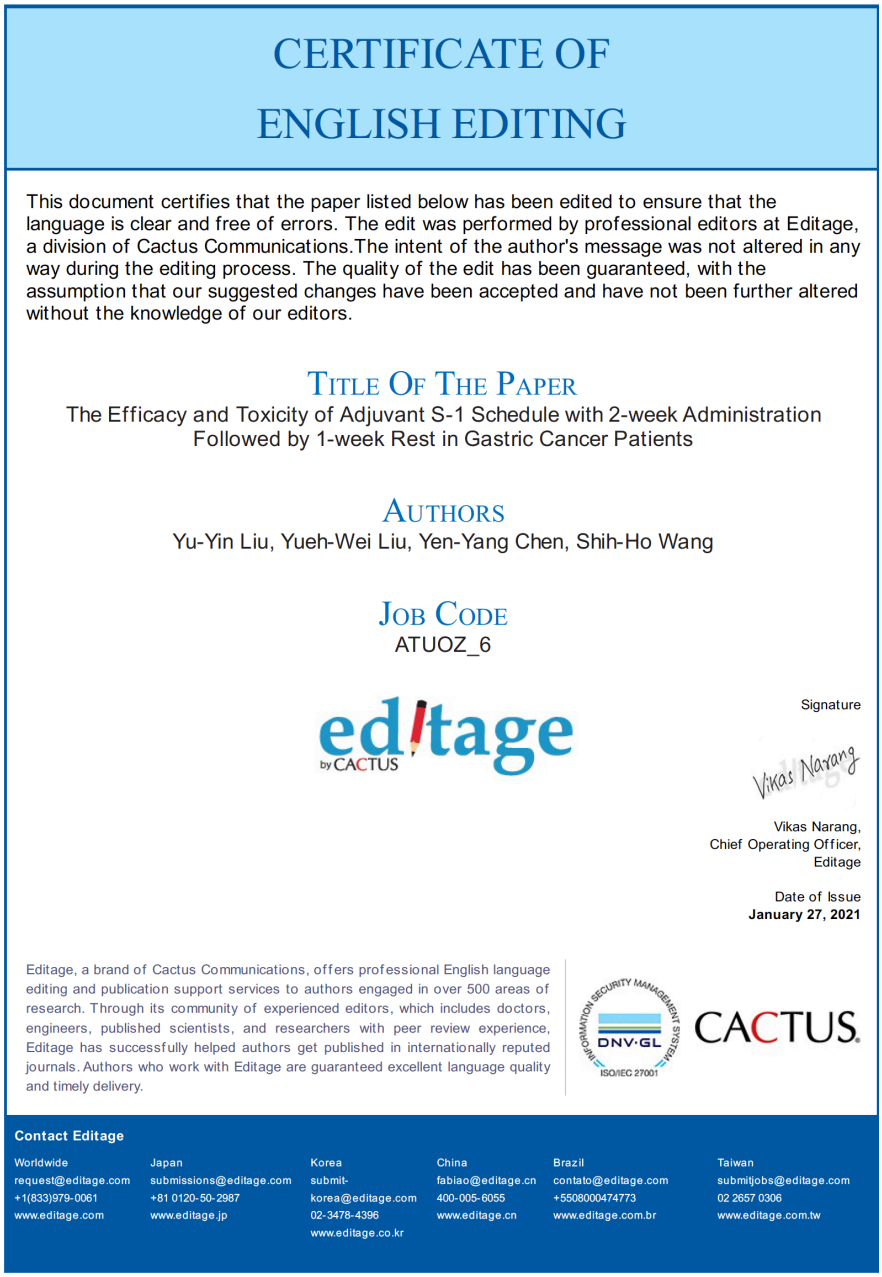
Introduction/*third paragraph*, **page 7, line 69, 78 and 83**

References 5, 8, 9, 10, 11, 12 and 15

<< COMMENT 4 >>

English language of the paper is problematic. Please have the paper edit by native speakers after revisions. For example, line 104 “cohort analysis with retrospectively designed”.

- ANSWER: Thanks for your comments. According to your suggestion, we have modified our manuscript using a professional language editing service. Please evaluate it.



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TITLE OF THE PAPER

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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<< COMMENT 5 >>

Methodology. Data collected on the clinical characteristics of included patients are simple. The authors also need to briefly describe how the patients were followed up. For outcome assessment, the definition of completion is necessary. Please also indicate the clinical research design of this study at the beginning of this part.

- ANSWER: Thanks for your comments. According to your suggestions, we have added the description about how patients were followed up, including the duration of hematologic/non-hematologic tests and image studies, principle of

dose reduction, and document of side effects. The definition of completion was also added according to previous published studies. In addition, we also added the description of the study designed. These descriptions were all added in the Methods section. Please evaluate it.

Methods/*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……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 one 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 mg to 100 mg or 100 mg 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 five years postoperatively. Patients visited the outpatient clinic for S-1 and underwent hematologic tests and assessments of clinical symptoms every 3–6 weeks for one year after surgery. Abdominal CT was performed every 3–6 months after surgery and panendoscopy was performed every six months during the first two 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.

References

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- CHANGE: Methods/*Study design and S-1 treatment*, **page 10, line 132, 140, 142, 146 and 152**
References 22

<< COMMENT 6 >>

Statistics. Line 167-168, log-rank test can not be used for estimate DFS and OS.

- ANSWER: Thanks for your comments. We have revised the description and deleted the term of "log-rank test" in our manuscript according to your suggestion. Please evaluate it.

Methods/*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. (**delete**: log-rank tests)

- CHANGE: Methods/*Statistical analysis*, page 12, line 164