Can S-1 replace fluorouracil for advanced gastric cancer? A PRISMA-compliant systematic review and meta-analysis

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Abstract

It remains to be seen whether S-1 can be a replacement for infusional fluorouracil (5-FU) for advanced gastric cancer (AGC). The aim of this study was to compare the efficacy and safety of S-1 with 5-FU in AGC.

PubMed and Cochrane Library were searched. Randomized controlled trials and meta-analyses comparing S-1 with 5-FU for AGC were eligible. Meta-analysis was performed using RevMan 5.2.

Seven trials involving 2443 patients were included. Compared with 5-FU, S-1 showed no significant prolongation of overall survival (OS) (hazard ratio [HR] = 0.91, 95% confidence interval [CI] [0.83–1.01], P = 0.07) and progression-free survival (HR = 0.89, 95% CI [0.70–1.13], P = 0.35), but longer time to treatment failure (HR = 0.74, 95% CI [0.56–0.97], P = 0.03). The objective response rates were comparable (risk ratio [RR] = 1.36, 95% CI [0.95, 1.96], P = 0.10). Regarding treatment-related deaths and hematological toxicities, there was significant heterogeneity between Asian and non-Asian trials, and subgroup analysis was applied. In Asian patients, there was a significant increase in hematological toxicities such as leukopenia (grade 1–4: RR = 1.22, 95% CI [1.08, 1.37], P = 0.001; grade 3–4: RR = 2.21, 95% CI [1.52, 3.21], P < 0.0001), neutropenia (grade 1–4: RR = 1.29, 95% CI [1.11, 1.48], P = 0.0005; grade 3–4: RR = 1.87, 95% CI [1.11, 3.17], P = 0.02), and thrombocytopenia (grade 1–4: RR = 1.71, 95% CI [1.22, 2.41], P = 0.002) in S-1-containing regimens compared with 5-FU-containing regimens, but without significant difference in treatment-related mortality rate (risk difference [RD] = 0.00, 95% CI [−0.01, 0.01], P = 0.68). In non-Asian patients, S-1-containing regimens were, however, associated with significantly fewer treatment-related deaths (RD = −0.02, 95% CI [−0.05, −0.00], P = 0.04), as well as less grade 1–4 and grade 3–4 hematological toxicities except anemia. There was no significant heterogeneity in nonhematologic toxicities between Asian and non-Asian trials. Lower incidence of grade 1–4 nausea, diarrhea, mucositis, grade 3–4 mucositis, increased creatinine, and decreased calculated creatinine clearance was observed in S-1-containing regimens.

S-1 could not improve OS, but increase some hematological toxicities in Asian patients. Therefore, special attention on hematological toxicities should be paid to Asian patients because S-1 is administered on an outpatient basis.

Abbreviations: 5-FU = fluorouracil, AEs = adverse events, AGC = advanced gastric cancer, CI = confidence interval, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QOL = quality of life, RCTs = randomized controlled trials, RD = risk difference, RR = risk ratio, TTF = time to treatment failure, TTP = time to progression

Keywords: Efficacy, fluorouracil, heterogeneity, meta-analysis, S-1, stomach neoplasms, toxicity

1. Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide. Because an early detection strategy through population-based screening is not yet widely practiced, the majority of patients are diagnosed with advanced disease. Surgical resection is the only treatment modality that is potentially curative for patients with local or locoregional disease. However, palliative chemotherapy should be considered for patients with unresectable locally advanced, metastatic, or recurrent disease, as it prolongs overall survival (OS) and improves quality of life (QOL) compared with best supportive care alone.

At present, infusional fluorouracil (5-FU) remains the mainstay for the treatment of advanced gastric cancer (AGC) due to its broad antitumor activity, as well as its synergism with other anticancer drugs. Nevertheless, its efficacy is relatively low, whereas its hematological and gastrointestinal toxicities are relatively common. S-1 is a novel oral fluoropyrimidine, comprising tegafur, gimeracil, and oteracil in a molar ratio of 1:0:4:1. Tegafur is a pro-drug of 5-FU and converted into 5-FU after absorption; gimeracil prolongs the half-life of 5-FU by...
decreasing its degradation in the liver; and oteracil improves gastrointestinal tolerability through decreasing 5-FU phosphorylation in the gastrointestinal tract.\[^{[4]}\]

Data from a series of phase II studies of S-1-containing regimens showed promising efficacy and favorable toxicity profiles.\[^{[5]}\] Based on the evidence obtained by the Japan Clinical Oncology Group trials, S-1 plus cisplatin has been recommended as the first-line regimen for AGC in Japan.\[^{[6]}\] In addition, more randomized trials outside of Japan comparing S-1 with 5-FU in mono or combined therapies have been carried out in recent years, with not completely consistent results regarding the efficacy and safety of these 2 treatments. It remains to be seen whether S-1 can be a replacement for infusional 5-FU.

A published meta-analysis of 4 trials indicated that S-1-based therapy showed better OS and nearly equivalent objective response rate (ORR) and safety profiles, compared with 5-FU-based therapy.\[^{[6]}\] After careful reading of the full text, we, however, found that this meta-analysis contained duplicate material, which led to unreliable results and conclusions. During our preparation of this manuscript, another meta-analysis including 6 trials reported similar results to the previous one.\[^{[7]}\] However, a few trials were not included and some pivotal information, such as heterogeneity between Asian and non-Asian, has been neglected in these analyses. In addition, the results of some trials have been updated recently. Therefore, we considered that it was deemed important to finish this meta-analysis to clarify the issue.

2. Materials and methods

Because no individual patient data were involved in this systematic review and meta-analysis, ethical approval from an ethics committee was not required.

2.1. Search strategy

Two reviewers (X-DC and F-QH) independently searched the following online electronic databases: PubMed and Cochrane Library using the following search terms: (((((((((gastric cancer) OR gastric carcinoma) OR gastric adenocarcinoma) OR stomach cancer) OR stomach carcinoma) OR stomach adenocarcinoma)) OR ((((((esophagogastric junction cancer) OR esophagogastric junction carcinoma) OR esophagogastric junction adenocarcinoma) OR gastroesophageal junction cancer) OR gastroesophageal junction carcinoma) OR gastroesophageal junction adenocarcinoma)) AND ((S-1)[Title/Abstract]) OR TS-1 [Title/Abstract])) OR random*). Searches were updated until December 2015. After identifying relevant citations, the abstracts of these studies were read to decide if the studies were eligible. The full text was retrieved when the information in the title and/or abstract seemed to meet the objective of this review. A manual search of reference lists of studies was conducted to identify any relevant articles not found in the computerized search.

2.2. Inclusion and exclusion criteria

Randomized controlled trials (RCTs) comparing S-1-containing chemotherapy with 5-FU-containing chemotherapy, mono or combined chemotherapy with S-1 versus 5-FU, and not confounded by additional agents or interventions (i.e., the experimental and control arms in the combined chemotherapy differed only in S-1 and 5-FU) were eligible for inclusion. Abstracts or unpublished work with sufficient information were also included. Included patients were diagnosed with histologically confirmed unresectable, recurrent, or metastatic gastric or esophagogastric junction carcinoma. Reports of survival results, response rates, or toxicities were mandatory for inclusion. Studies containing duplicate material were excluded, and the studies containing the best documented data were included for analysis.

2.3. Selection, quality assessment, and data extraction

Two reviewers (X-DC and F-QH) independently read the title and abstract of each searched citation to select eligible studies for further assessment. The full text of potentially eligible citations were retrieved and evaluated for inclusion. The Jadad scale was used to assess the quality of the selected studies.\[^{[8]}\] Two reviewers independently extracted all relevant information in a data collection form, including study characteristics (author, country, sample size, regimen details, and methodological characteristics), efficacy, and safety data.

2.4. Outcomes of interest

The primary efficacy endpoint used for this study was OS. Secondary efficacy measures were endpoints based on tumor assessments, including ORR, defined as the sum of partial and complete response rates assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), progression-free survival (PFS), time to treatment failure (TTF), and time to progression (TTP). Safety analysis was based on adverse events (AEs), including treatment-related deaths and toxicities graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE).

2.5. Statistical analysis

Statistical analyses of the pooled hazard ratio (HR) for OS, PFS, and TTF, the risk ratio (RR) or risk difference (RD) for ORR and AEs were calculated using Review Manager (RevMan) Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). We also compared the pooled estimates of OS and ORR for subgroups stratified by region (Asia vs non-Asia) and regimen (different combined cytotoxic drugs). Statistical heterogeneity was evaluated by the $\chi^2$ test and the $I^2$ statistic and was considered high when $P < 0.1$ or $I^2 > 50\%$. In meta-analysis, the fixed-effects method was used when the statistical heterogeneity was low, and the random-effects model and subgroup analysis were applied when it was high. The result stability was evaluated by performing a sensitivity analysis, in which one study was removed at a time. The presence of publication bias was evaluated by using the Begg and Egger tests in StataSE version 12.0 (Stata Corporation, College Station, TX).\[^{[9,10]}\] An HR $< 1$ indicated a favorable outcome of S-1-containing regimens for OS, PFS, and TTF. A RR $> 1$ or RD $> 0$ indicated a favorable ORR or more AEs in S-1-containing regimens. A 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

The literature search and selection procedure are shown in Figure 1. A total of 7 RCTs were eligible for analysis, including 5 full texts\[^{[11–15]}\], 1 abstract from ASCO Annual Meeting\[^{[16]}\], and 1 abstract from the ECCO/ESMO Congress.\[^{[17]}\] The main characteristics of the included trials were shown in Table 1. Six studies were performed in East Asia (3 in Japan\[^{[12,14,17]}\] and 3
in China\cite{11,15,16}, and the remaining study was a non-Asian global phase III trial performed in 24 countries\cite{13}. All studies were multicenter in nature, involving 8 to 146 centers. Of the 2443 patients in those studies, 1236 patients received S-1-containing chemotherapy and 1207 patients received 5-FU-containing chemotherapy. The sample size of individual trials ranged from 147 to 1029 patients. Two studies compared S-1 alone with 5-FU alone (S-1 vs 5-FU),\cite{14,17} 3 compared S-1 plus cisplatin with 5-FU plus cisplatin (SP vs FP),\cite{13,15,16} and 2 compared S-1 plus paclitaxel with 5-FU plus paclitaxel (SPtx vs FPtx).\cite{11,12} Regimens were similar with respect to doses and schedules in every trial. There were no significant differences in the baselines between S-1-containing and 5-FU-containing groups in these studies as reported.

3.1. Efficacy

3.1.1. OS. Six studies reported OS data. Median OS ranged from 8.3 to 15.2 months in the S-1-containing groups and 7.9 to 14.2 months in the 5-FU-containing groups (Table 2).\cite{12–17} Two studies reported that S-1-containing regimens were superior to 5-FU-containing regimens\cite{14,16}, whereas the others reported that S-1-containing regimens were comparable or noninferior to 5-FU-containing regimens. The meta-analysis showed no statistically significant improvement of OS with S-1-containing regimens versus 5-FU-containing regimens (HR = 0.91, 95% confidence interval [CI] [0.83–1.01], \( P = 0.07 \); \( P \) of heterogeneity = 0.18, \( I^2 = 34\% \); Fig. 2). The subgroup analyses of OS by region (Asia and non-Asia) and regimen (S-1 vs 5-FU, SP vs FP, and SPtx vs FPtx) found no differences, and tests for subgroup differences showed no significant difference in heterogeneity among subgroups (Figs. 3 and 4, respectively).

3.1.2. PFS. Four studies reported PFS, which ranged from 3.5 to 6.0 months in the S-1-containing groups and 2.9 to 5.5 months in the 5-FU-containing groups (Table 2).\cite{11,13,14,17} Two Asian
Table 1

Characteristics of included trials.

| Study                  | Country   | Centers | Participants (M/F) | Intervention   | Scheme of chemotherapy | Endpoints | Jadad scores |
|-----------------------|-----------|---------|-------------------|----------------|-----------------------|-----------|--------------|
| Huang et al (2013)    | China     | 14      | 119 (89/30)       | S-1            | S-1 80–120 mg/d d1-14, PTX 60 mg/m² d1, 8, 15
|                       |           |         |                   | FPU (con.)     |                       | DCR, PFS, TTF, safety | 3 |
|                       |           |         |                   | FPU (con.)     |                       |                       | 
|                       |           |         |                   | FPU (con.)     |                       |                       | 
|                       |           |         |                   | FPU (con.)     |                       |                       | 
| Nishikawa et al (2012) | Japan     | 8       | 40 (23/12)        | S-1            | S-1 80 mg/m² d1-28+q4w until progression, followed by PTX 80 mg/m² d1, 8, 15
|                       |           |         |                   | FPU (seq.)     |                       | OS, TTF, ORR, safety | 3 |
|                       |           |         |                   | FPU (seq.)     |                       |                       | 
|                       |           |         |                   | FPU (seq.)     |                       |                       | 
| Jin et al (2008)      | China     | 15      | 74 (55/19)        | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1/q4w
| Boku et al (2009)     | Japan     | 34      | 234 (176/58)      | S-1            | S-1 80 mg/m² d1-28+q6w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-28+q6w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-28+q6w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-28+q6w
| Li et al (2015)       | China     | 120     | 80 (60/20)        | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1-4, q5w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1-4, q5w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1-4, q5w
|                       |           |         |                   | S-1            | S-1 80 mg/m² d1-21, DDP 20 mg/m² iv d1-4, q5w
| Jin et al (2008)      | China     | 15      | 73 (61/12)        | S-1            | S-1 40–60 mg bid d1-21, DDP 60 mg/m² iv q1-4,q5w
|                       |           |         |                   | S-1            | S-1 40–60 mg bid d1-21, DDP 60 mg/m² iv q1-4,q5w
|                       |           |         |                   | S-1            | S-1 40–60 mg bid d1-21, DDP 60 mg/m² iv q1-4,q5w
|                       |           |         |                   | S-1            | S-1 40–60 mg bid d1-21, DDP 60 mg/m² iv q1-4,q5w
| Sawaki et al (2009)   | Japan     | 146     | 521 (382/139)     | S-1            | S-1 50 mg/m² d1-21, DDP 75 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 50 mg/m² d1-21, DDP 75 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 50 mg/m² d1-21, DDP 75 mg/m² iv d1/q4w
|                       |           |         |                   | S-1            | S-1 50 mg/m² d1-21, DDP 75 mg/m² iv d1/q4w

Table 2

Detailed information of OS, PFS, TTF, and TTP reported by some included trials.

| Study                  | Participants | OS [95% CI], mo | PFS [95% CI], mo | TTF/TTP [95% CI], mo |
|-----------------------|--------------|-----------------|-----------------|----------------------|
| Huang et al (2013)    | 119 S-1 110 S-FU | 5.0             | 4.2             | 16 days
|                       |              | HR=0.641 [0.473-0.868], P=0.004 | HR=0.641 [0.473-0.868], P=0.004 |
| Nishikawa et al (2012) | 80 S-1 77 S-FU | 15.2 [11.4–19.0] | 14.2 [9.6–18.7] | 20 days
|                       |              | HR=0.96 [0.67–1.39], P=0.83 | HR=0.96 [0.67–1.39], P=0.83 |
| Jin et al (2010)      | 521 S-1 508 S-FU | 8.6 [7.9–9.5] | 7.9 [7.2–8.5] | No difference
|                       |              | HR=0.92 [0.80–1.05], P=0.20 | HR=0.92 [0.80–1.05], P=0.20 |
| Boku et al (2009)     | 234 S-1 234 S-FU | 11.4 [6.4–21.3] | 10.8 [5.7–17.7] | 3.8
|                       |              | HR=0.83 [0.68–1.00], P=0.0253 | HR=0.83 [0.68–1.00], P=0.0253 |
| Li et al (2015)       | 120 S-1 116 S-FU | 10.00 [8.59–14.52] | 10.46 [8.92–13.84] | 2.3
|                       |              | HR=1.05 [0.71–1.54], P=0.82 | HR=1.05 [0.71–1.54], P=0.82 |
| Jin et al (2008)      | 74 S-1 73 S-FU | 14.2 [12.0–] | 10.2 [7.8–] | 0.51
|                       |              | HR=0.52 [0.30–0.92], P=0.038 | HR=0.52 [0.30–0.92], P=0.038 |
| Sawaki et al (2009)   | 88 S-1 89 S-FU | 8.3 [6.9–10.4] | 10.3 [8.1–12.9] | 0.52
|                       |              | HR=1.19 [0.85–1.67], P=0.31 | HR=1.19 [0.85–1.67], P=0.31 |

OS = overall survival, PFS = progression-free survival, TTF = time to treatment failure, TTP = time to progression.

† Data obtained through correspondence with the original investigators.

‡ Interquartile range.
studies reported that S-1-containing regimens significantly prolonged PFS compared with 5-FU-containing regimens,\(^{[11,14]}\) whereas the meta-analysis showed there were no significant benefits in PFS for the S-1-containing groups (HR = 0.89, 95% CI [0.70–1.13], \(P = 0.35\); \(P\) of heterogeneity = 0.003, \(I^2 = 79\%\); Fig. 5).

### 3.1.3. TTF

Six studies reported TTF, which ranged from 2.8 to 5.2 months in the S-1-containing groups and 2.8 to 3.8 months in the 5-FU-containing groups (Table 2).\(^{[11–14,16,17]}\) One study reported that no difference in TTF was observed between S-1-containing and 5-FU-containing regimens but did not provide exact data for meta-analysis.\(^{[12]}\) Another study reported the Kaplan-Meier curve and HR of TTF; however, the median of TTF obtained through correspondence with the original investigators was only 16 days and 20 days which were observed in 17 patients and 19 patients of the S-1-containing and 5-FU-containing groups, respectively.\(^{[11]}\) Consequently, these 2 studies were excluded from the meta-analysis. The pooled data of the remaining 4 studies by the random-effects model were significantly in favor of the S-1-containing group (HR = 0.74, 95% CI [0.56–0.97], \(P = 0.03\); \(P\) of heterogeneity = 0.0004, \(I^2 = 84\%\); Fig. 6).

### 3.2. Safety

We compared grade 1–4 and grade 3–4 toxicities in both groups according to reported information (Tables 4 and 5). The major toxicities of S-1-containing regimens were hematological toxicities including anemia, leukopenia, neutropenia, febrile...
neutropenia, thrombocytopenia, and gastrointestinal toxicities including nausea, vomiting, anorexia, diarrhea, constipation, and mucositis. Other relatively common toxicities were liver impairment (increased aminotransferases and bilirubin), renal impairment (increased creatinine and decreased calculated creatinine clearance), fatigue, infection, weight loss, and neuropathy.

3.2.1. Treatment-related deaths. Treatment-related deaths were reported in 4 studies.\(^ {11,13–15} \) The accumulated treatment-related mortality rate in Asian patients was 0.4% (2/473) in the S-1-containing group versus 0.2% (1/460) in the 5-FU-containing group, without significant difference (RD = 0.00, 95% CI [−0.01, 0.01]; P = 0.68; Table 4); however, the mortality rate

| Study or Subgroup | log(Hazard Ratio) | SE Total | Total Weight | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|----------|--------------|--------------------------------|
| Boku N, 2009      | -0.1863          | 0.1017   | 234          | 234 57.6% 0.83 [0.68, 1.01] |
| Sawaki A, 2009    | 0.1744           | 0.1734   | 88           | 89 42.4% 1.19 [0.85, 1.67] |
| Subtotal (95% CI) | 322              | 323      | 100.0%       | 0.97 [0.68, 1.37] |

Heterogeneity: Tau\(^ 2 = 0.04; Chi^2 = 3.22, df = 1 (P = 0.07); I^2 = 69\% 
Test for overall effect: Z = 0.19 (P = 0.85)

1.3.2 SP vs. FP

Jin M, 2008        | -0.0461          | 0.2858   | 74           | 73 18.1% 0.52 [0.30, 0.92] |
Ajani JA, 2010     | -0.0834          | 0.0713   | 521          | 508 53.5% 0.92 [0.80, 1.06] |
Li YH, 2015        | 0.045            | 0.1984   | 120          | 116 28.5% 1.05 [0.71, 1.54] |
Subtotal (95% CI)  | 715              | 697      | 100.0%       | 0.86 [0.65, 1.14] |

Heterogeneity: Tau\(^ 2 = 0.03; Chi^2 = 4.24, df = 2 (P = 0.12); I^2 = 53\% 
Test for overall effect: Z = 1.03 (P = 0.30)

1.3.3 SPt vs. FPtx

Nishikawa K, 2012  | -0.0392          | 0.1835   | 80           | 77 100.0% 0.96 [0.67, 1.38] |
Subtotal (95% CI) | 80               | 77       | 100.0%       | 0.96 [0.67, 1.38] |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)

Figure 4. Forest plot of subgroup analysis of overall survival by regimen. SP = S-1 plus cisplatin, FP = 5-FU plus cisplatin, SPtx = S-1 plus paclitaxel, FPtx = 5-FU plus paclitaxel.

Figure 5. Forest plot of progression-free survival associated with the S-1-containing chemotherapy compared with the 5-FU-containing chemotherapy.

| Study or Subgroup | log(Hazard Ratio) | SE Total | Total Weight | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|----------|--------------|--------------------------------|
| Boku N, 2009      | -0.4447          | 0.1551   | 119          | 110 21.8% 0.64 [0.47, 0.87] |
| Ajani JA, 2010    | -0.2614          | 0.0943   | 234          | 234 27.8% 0.77 [0.64, 0.93] |
| Sawaki A, 2009    | 0.2744           | 0.1688   | 98           | 98 20.5% 1.32 [0.94, 1.84] |
| Total (95% CI)    | 962              | 941      | 100.0%       | 0.89 [0.70, 1.13] |

Heterogeneity: Tau\(^ 2 = 0.05; Chi^2 = 14.29, df = 3 (P = 0.003); I^2 = 79\% 
Test for overall effect: Z = 0.94 (P = 0.35)

Figure 6. Forest plot of time to treatment failure associated with the S-1-containing chemotherapy compared with the 5-FU-containing chemotherapy.

neutropenia, thrombocytopenia, and gastrointestinal toxicities including nausea, vomiting, anorexia, diarrhea, constipation, and mucositis. Other relatively common toxicities were liver impairment (increased aminotransferases and bilirubin), renal impairment (increased creatinine and decreased calculated creatinine clearance), fatigue, infection, weight loss, and neuropathy.
in non-Asian patients was 2.5% (13/521) in the S-1-containing group versus 4.9% (25/508) in the 5-FU-containing group, which was a significant difference (RD = –0.02, 95% CI [–0.05, –0.00], P = 0.04; Table 4). Testing for subgroup differences was then performed, showing a significant difference in heterogeneity between Asian and non-Asian subgroups (P of heterogeneity = 0.04, I² = 76.5%).

### 3.3. Hematological toxicities

The profile of hematological toxicities was distinct between Asian and non-Asian trials (Table 4). Testing for subgroup differences demonstrated significant difference in heterogeneity between Asian and non-Asian subgroups. In Asian patients, there was a significant increase of hematological toxicities in S-1-containing regimens such as leukopenia (grade 1–4: RR = 1.22, 95% CI [1.08, 1.37], P = 0.001; grade 3–4: RR = 2.21, 95% CI [1.52, 3.21], P < 0.0001), neutropenia (grade 1–4: RR = 1.29, 95% CI [1.11, 1.48], P = 0.0005; grade 3–4: RR = 1.87, 95% CI [1.11, 3.17], P = 0.02), and thrombocytopenia (grade 1–4: RR = 1.71, 95% CI [1.22, 2.41], P = 0.002). Conversely, in non-Asian patients, S-1-containing regimens were found to be associated with lower toxicities for leukopenia (grade 1–4: RR = 0.72, 95% CI [0.66, 0.79], P < 0.0001; grade 3–4: RR = 0.41, 95% CI [0.32, 0.53], P < 0.0001), neutropenia (grade 1–4: RR = 0.74, 95% CI [0.68, 0.80], P < 0.0001; grade 3–4: RR = 0.51, 95% CI [0.44, 0.59], P < 0.0001), febrile neutropenia (grade 1–4: RR = 0.28, 95% CI [0.14, 0.56], P = 0.0003; grade 3–4: RR = 0.05, 95% CI [–0.08, –0.03], P < 0.0001), and thrombocytopenia (grade 1–4: RR = 0.73, 95% CI [0.63, 0.84], P < 0.0001; grade 3–4:...
RR = 0.62, 95% CI [0.43, 0.89], \( P = 0.009 \). However, no significant difference in anemia was found in both subgroups.

### 3.4. Gastrointestinal toxicities

With regard to nonhematological toxicities, there was no significant heterogeneity between Asian and non-Asian subgroups. Gastrointestinal toxicities were frequent in both groups (Table 5). The incidence of nausea, vomiting, anorexia, diarrhea, and constipation demonstrated no significant differences between groups except that S-1-containing regimens were associated with a significantly decreased incidence of grade 1–4 nausea (RR = 0.80, 95% CI [0.64, 1.00], \( P = 0.05 \)) and grade 1–4 diarrhea (RR = 0.79, 95% CI [0.67, 0.94], \( P = 0.006 \)) (Table 4). Of note, S-1-containing regimens were associated with less frequent and less severe mucositis (stomatitis and/or mucosal inflammation), with an incidence of grade 1–4 mucositis of 10.1% versus 60.2% with 5-FU-containing regimens (RR = 0.17, 95% CI [0.13, 0.22], \( P < 0.001 \)), and grade 3–4 of 1.9% versus 14.7%, respectively (RR = 0.23, 95% CI [0.06, 0.88], \( P = 0.03 \)).

### 3.5. Sensitivity analysis

Sensitivity analysis showed that the corresponding pooled HRs and ORRs were not significantly altered when one study was removed at a time, suggesting stability of the results.

### 3.6. Publication bias

Begg funnel plot and Egger test were performed to assess the publication bias of the analyzed studies. The shapes of the Begg funnel plots did not reveal evidence of obvious asymmetry (\( P = 1.00 \) and 0.76 for OS and ORR, respectively; Fig. 7). Egger test was then used to provide statistical evidence of funnel plot symmetry. The results still suggested no evidence of publication bias (\( P = 0.91 \) and 0.20 for OS and ORR, respectively).

### 4. Discussion

Five meta-analyses were identified in the literature search.\[16,17,18\] The main characteristics and results of these analyses were compared with the present study in Table 6. Although 2 published meta-analyses showed the superiority of S-1-containing regimens compared with 5-FU-containing regimens in terms of OS, one contained duplicate material\[19\] and the other missed a trial which was included in the present analysis.\[20\] In the present study, the pooled data revealed no significant improvement in OS for S-1-containing regimens (HR = 0.91, 95% CI [0.83–1.01], \( P = 0.07 \)). It seems difficult to draw firm data-driven conclusion as to survival benefit of S-1. The median OS of S-1 monotherapy was approximately 11 months and the addition of other cytotoxic drugs, such as cisplatin,\[16,21\] oxaliplatin,\[22\] paclitaxel,\[23\] docetaxel,\[24,25\] or irinotecan\[26,27\] to S-1, even prolonged median OS beyond 12 months. Several trials comparing these doublets with S-1 monotherapy were conducted.
and demonstrated that the doublets resulted in a longer OS than that resulting from S-1 monotherapy.\textsuperscript{[16,21,23,25]} However, there are no data indicating which doublets are superior as first-line treatments for AGC.\textsuperscript{[28–30]} Therefore, we suggest that the emphasis should be on further developing S-1 with different cytotoxic drugs and/or biologic agents to anticipate the prolongation of OS in patients with AGC.

Regarding endpoints based on tumor assessments, the pooled data showed that there were no significant differences in ORR and PFS between the 2 groups, whereas S-1-containing regimens were associated with much longer TTF than 5-FU-containing regimens. However, there was significant heterogeneity among trials; therefore, these results should be interpreted with caution. The subgroup meta-analyses showed that there was higher ORR in Asian patients with S-1-containing regimens than 5-FU-containing regimens, but no such difference was found in non-Asian patients. Different stage presentation may affect the efficacy; however, there was no obvious difference in the extent of disease between Asian and non-Asian patients. The profile of stage presentation was remarkably similar in all trials, that is, the majority (above 95%) of patients had metastatic disease and over two-thirds had more than one site of metastasis. In fact, according to the analyzed data in the present study (Tables 2 and 3), the efficacy of S-1 was closely comparable between Asian and non-Asian patients. The median OS was 8.6 months in non-Asian patients versus 8.3 to 15.2 months in Asian patients, PFS 4.8 months versus 3.5 to 5.0 months, TTF 3.8 months versus 2.8 to 5.2 months, ORR 29.1% versus 31.4%; nevertheless, the ORR of 5-FU-containing regimens was evidently high in non-Asian patients (31.9% vs 19.6%), which might be responsible for the difference.

With respect to safety profiles, S-1 monotherapy had a low incidence of grade 3–4 toxicities (usually <5% for each toxicity);\textsuperscript{[31]} however, the addition of other cytotoxic drugs significantly increased the incidence of grade 3–4 toxicities, which remained manageable.\textsuperscript{[16,21,23,25,27]} It is noteworthy that there was significant heterogeneity in the incidence of treatment-related deaths and hematological toxicities between Asian and non-Asian patients. The reported treatment-related mortality was <1% in Asian patients, but was >2.5% in non-Asian patients. Treatment-related deaths were mainly caused by myelosuppression and infection.\textsuperscript{[11,13]} Accordingly, the incidences of grade 3–4 leukopenia, neutropenia, and febrile neutropenia were markedly higher in non-Asian patients, especially in those assigned to 5-FU-containing regimens. Actually, according to the data from Table 4, the incidences of hematological toxicities for S-1-containing regimens were comparable between Asian and non-Asian patients; by contrast, the incidences for 5-FU-containing regimens were relatively low in Asian patients whereas remarkably high in non-Asian patients. As a result, the incidences of hematological toxicities in Asian patients were significantly higher in S-1-containing regimens than those in 5-FU-containing regimens. Conversely, the rates of hematological toxicities in non-Asian patients were significantly less frequent in S-1-containing regimens than 5-FU-containing regimens.

The reason for these differences is complicated and may be related to geographic region, dose, and schedule of cytotoxic drugs and gene polymorphism. A meta-analysis indicated that the Asian trials were associated with lower incidences of grade 3–4 neutropenia and febrile neutropenia, and concluded that geographic region was an independent predictor of safety in chemotherapy for gastric cancer.\textsuperscript{[32]} The dose and schedule of cytotoxic drugs varied among studies due to the individual distinctions and practice culture in different regions. In every chemotherapy cycle, the daily dose of S-1 was usually 80mg/m\textsuperscript{2} in Asian patients versus 50mg/m\textsuperscript{2} in non-Asian patients; the total dose of S-5U varied widely among studies, from 2500mg/m\textsuperscript{2} to 4000mg/m\textsuperscript{2} in Asian patients versus 5000mg/m\textsuperscript{2} in non-Asian patients. We observed that the non-Asian patients were significantly less frequent in S-1-containing regimens than 5-FU-containing regimens.

Figure 7. Begg funnel plot of publication bias test: (A) overall survival (OS) and (B) objective response rate (ORR). Each point represents a separate study for the indicated association; log = natural logarithm, s.e. = standard error.

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### Table 6
Comparisons of the main characteristics and results of the identified analyses with the present study.

| Study | Huang et al (2011) | Wu et al (2012) | Cao et al (2014) | Liu et al (2014) | Li et al (2014) | Present analysis |
|-------|-------------------|----------------|-----------------|-----------------|----------------|-----------------|
| No. of trials | 4 | 3 | 3 | 3 | 6 | 7 |
| Interventions | 2 S-1 vs 5-Fu; 2 SP vs FP | 4 SP vs FP | 1 S-1 vs 5-Fu; 2 SP vs FP; 1 SPtx vs FPtx | 3 SPtx vs FPtx | 2 S-1 vs 5-Fu; 3 SP vs FP; 2 SPtx vs FPtx | 2 S-1 vs 5-Fu; 3 SP vs FP; 2 SPtx vs FPtx |
| Efficacy measures | | | | | | |
| OS | HR = 0.87 [0.79–0.96], P = 0.007; R_h = 0.586, I² = 0% | NR | NR | -- | HR = 0.87 [0.79–0.96], P = 0.007; R_h = 0.586, I² = 0% | -- |
| PFS | NR | NR | NR | -- | NR | -- |
| TTF | NR | NR | NR | -- | HR = 0.73 [0.53–1.00], P = 0.05; R_h = 0.0004, I² = 84% | -- |
| ORR | OR = 1.25 [0.31–5.09], P = 0.754; R_h = 0.001, I² = 90.5% | OR = 1.58 [0.76–3.29], P = 0.22; R_h = 0.03, I² = 66% | OR = 2.31 [1.29–4.13], P = 0.005; R_h = 0.202, I² = 69.5% | OR = 1.55 [0.53–2.19], P = 0.84; R_h = 0.02, I² = 78% | OR = 1.55 [0.87–2.77], P = 0.14; R_h < 0.0001, I² = 83% | OR = 1.36 [0.95, 1.96], P = 0.10; R_h < 0.0001, I² = 80% |
| Safety profiles | | | | | | |
| Treatment-related deaths | OR = 1.84 [0.95–3.54], P = 0.068; R_h = 0.279, I² = 14.6% | NR | OR = 1.15 [0.39–3.45], P = 0.798 | -- | NR | -- |
| Hematological | Less in S-1 group: grade 3–4 neutropenia (OR = 0.33 [0.25–0.44], P = 0.004) | Less in S-1 group: grade 3–4 thrombocytopenia (OR = 0.58 [0.40–0.85], P = 0.004) | More in S-1 group: grade 3–4 thrombocytopenia (OR = 2.30 [1.40–3.77], P = 0.001) | Equivalent | Less in S-1 group: grade 3–4 stomatitis (OR = 0.60 [0.42–0.88], P = 0.008) | Significant difference in heterogeneity between Asian and non-Asian subgroups |
| Gastrointestinal | Equivalent | Less in S-1 group: grade 3–4 nausea/vomiting (OR = 0.70 [0.32–0.95], P = 0.02) | More in S-1 group: grade 3–4 diarrhea (OR = 3.18 [1.54–6.57], P = 0.002); less in S-1 group: grade 3–4 nausea (OR = 0.69 [0.48–1.00], P = 0.049) | Less in S-1 group: grade 3–4 nausea (OR = 0.60 [0.43–0.82], P = 0.001) and vomiting (RR = 0.55 [0.33–0.91], P = 0.02) | Less in S-1 group: grade 3–4 stomatitis (OR = 0.22 [0.05–0.9], P = 0.03) | Less in S-1 group: grade 1–4 nausea, diarrhea, mucositis |

-- cannot be calculated, FP = fluorouracil (5-FU) plus DDP, FPtx = FP plus PTX, NR = not reported, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, R_h = P of heterogeneity, R_h = P of subgroup differences, SP = S-1 plus cisplatin (DDP), SPtx = S-1 plus paclitaxel (PTX), TTF = time to treatment failure.
Asian patients would be mainly attributed to higher doses of 5-FU and cisplatin in 5-FU-containing regimens. With respect to the nonhematological toxicities, S-1-containing regimens significantly reduced the frequency and severity of mucositis compared with S-5-FU-containing regimens. A grade 4 increase in total bilirubin was the only notable nonhematological toxicity observed more frequently in S-1-containing regimens. However, there were no differences with respect to grade 4 elevations in aminotransferases (ALT/AST) or reports of death due to drug-related hepatic toxicity, indicating that there was no evidence of direct hepatotoxicity by S-1.31,38 Ajani et al acknowledged that the significantly lower rate of renal function abnormalities, such as elevated serum creatinine and impairment of renal clearance in the cisplatin/S-1 arm, could be attributed to lower cisplatin dose (75 mg/m²) than in the cisplatin/infusional fluorouracil arm (100 mg/m²).13

Although the data on QOL and cost-effectiveness analysis were limited, S-1-containing regimens seemed to be associated with longer nonhospitalized survival, fewer hospitalizations for drug administration, and lower monetary costs. One abstract mentioned QOL as secondary endpoints, but no detailed data were reported.17 Because infusional chemotherapy is commonly performed with hospitalization, we would presume that the nonhospitalized survival reflects a patient’s benefit from a QOL point of view.13 Boku et al reported that S-1 was associated with longer nonhospitalized survival compared with 5-FU (9.3 [interquartile range 4.2–18.0] vs 7.2 [2.7–13.3] months, HR = 0.77, 95% CI [0.63–0.92], P = 0.0025).14 Moreover, Ajani et al reported that the total number of hospitalizations and percentage of patients hospitalized were lower and the median number of days hospitalized was shorter in S-1-containing arm.138 In addition to efficacy and safety concerns, expenditure on chemotherapy drugs has recently become a main concern. Unfortunately, few trials compared S-1 with 5-FU from an economic point of view. Only Boku et al offered some information in their discussion section, reporting that in Japan, economic point of view. Only Boku et al offered some information in their discussion section, reporting that in Japan, economic point of view. Only Boku et al offered some information in their discussion section, reporting that in Japan, the cost of S-1 was cheaper than that of 5-FU.14

Some limitations should be considered when interpreting the data presented here. First, 2 included studies were abstracts from international conferences with insufficient data on methodological and patient characteristics. In addition, many important estimates, such as PFS, TTF, TTP, and some AEIs, were not reported in many of the studies analyzed. These omissions might potentially limit detection of difference. Furthermore, heterogeneity problems were frequently found among the included studies and subgroups, which may have influenced our results. Therefore, we chose to use the random-effects model as well as subgroup analysis to calculate the estimates and explain the causes of heterogeneity, such as differences in geographic region, dose, and schedule of cytotoxic drugs. In addition, most of the studies included were performed in Asia, with only one non-Asian study. We noticed significant differences in efficacy and safety profiles, such as median OS, treatment-related mortality, and incidence of hematological toxicities. However, future studies are needed to determine the mechanism underlying this phenomenon.

In conclusion, S-1-containing regimens could not improve survival outcomes, but increase some hematological toxicities in Asian patients, compared with 5-FU-containing regimens. Therefore, special attention on hematological toxicities should be paid to Asian patients because S-1 is administered on an outpatient basis. Moreover, whether S-1 could provide advantages in terms of QOL and monetary costs needs to be clarified by further trials.

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