 Survival benefit from S-1 as compared to Fluorouracil in Asian patients with advanced gastrointestinal cancer: A meta-analysis

Chunxiang Cao,¹ Xunlei Zhang,² Meng Kuang,¹ Dongying Gu,¹ Mingliang He,³ Jinfei Chen¹ and Cuiju Tang¹

¹Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing; ²Department of Oncology, Nantong Tumor Hospital, Nantong; ³Stanley Ho Center for Emerging Infectious Diseases and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong

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Correspondence
Jinfei Chen and Cuiju Tang, Department of Oncology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing 210006, China.
Tel: +86-25-87726234; Fax: +86-25-87726234;
E-mails: tangcuiju2013@163.com; jinfeichen@sohu.com

Chunxiang Cao and Xunlei Zhang contributed equally to this work and share first authorship.

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Along with recent improvements in diagnostic and therapeutic modalities, the multidisciplinary management of cancer treatments has been explored to improve outcomes.¹–³ However, distant metastasis or recurrences require effective chemotherapies.⁴ 5-Fu has been a core anticancer agent for malignancies since it was introduced by Heidelberger et al.⁵ in 1957, and it has been widely used in international standard regimens for GI malignancies except etoposide, doxorubicin and cisplatin (EAP) therapy.

Gastric cancer and colorectal cancer, the two mainly discussed GI cancers in this paper, are the second and fourth highest causes of cancer-related death in the world.⁶ For advanced gastric cancer (AGS), there has been no standard palliative chemotherapy regimen worldwide, while palliative chemotherapy including 5-Fu, platin compounds, docetaxel and epirubicin has been proved to prolong survival time and improve quality of life compared with best support care.⁷ For mCRC, regimens of FOLFOX (5-Fu, leucovorin, and oxaliplatin) or FOLFIRI (5-Fu, leucovorin, and irinotecan) plus bevacizumab are being currently used as first line treatment.⁸–⁹ Although the regimens of AGS and mCRC are different, 5-Fu has been an important drug in both cancer chemotherapy regimens for decades.

5-Fu is usually administered by i.v. bolus or by continuous i.v. infusion. Although the latter route is the most efficient and least toxic, it is costly and inconvenient, and most importantly, catheter-related safety concerns emerge.¹⁰ Oral administration could avoid such iatrogenic issues, and the balance of cost and benefit has been discussed.¹¹,¹² S-1 is a fourth generation oral fluoropyrimidine containing tegafur, 5-chloro-2, 4-dihydroxy-pyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil. CDHP is a dihydroxypyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyltransferase (OPRT), reducing GI toxicities.¹³ Whether S-1 could replace 5-Fu has been hotly explored and discussed in recent years. The results from recent randomized phase II/III studies for AGS or mCRC have demonstrated that S-1 in combination with chemotherapies such as cisplatin, oxali-
Materials and Methods

Search strategy. We searched all published (as English-language full paper or abstract) and unpublished trials that compared S-1 with 5-Fu in the treatment of advanced GI cancer. The search was performed using PubMed and Proceedings of American Society of Clinical Oncology (ASCO) (1983 to December 2013), with various combinations of different terms: “S-1”, “5-Fluorouracil”, “randomized controlled trial”, “gastrointestinal cancer”, “gastric cancer”, “colorectal cancer”, “colon cancer”, and “rectal cancer”. References of selected articles and previous systematic reviews were checked for any other relevant trials.

Selection of trials. Trials had to fulfill the following inclusion criteria: (i) Asian patients with AGC or mCRC at baseline; (ii) prospective phase II and III RCTs; (iii) S-1 and 5-Fu were compared without confounding by additional agents or interventions (i.e., in the combination chemotherapy, the control and experimental arms had to differ only by S-1 or 5-Fu component).

Two independent reviewers (C.C. and X.Z.) assessed the eligibility of abstracts identified by the search. The full-text article of any trial that appeared to meet the inclusion criteria was retrieved for closer examination. If multiple publications of the same trial were retrieved, or if there were data inconsistencies between publications of the same trial, all publications were included, but only the most recent and the most informative data were used.

Quality assessment. The quantitative 5-point Jadad score was used to assess the quality of included trials based on the report of the methods and results of the studies.20

Data extraction. To avoid bias in the data extraction process, the same two reviewers (C.C. and X.Z.) independently extracted the data from the trials and compared results. The following information was extracted from each article: (i) publication details such as type of cancer, first author, year of publication, country, phase of study, and form of publication (full/abstract); (ii) information of treatment such as chemotherapy regimens, treatment line, median OS, median PFS, ORR and toxicity; (iii) characteristics of patients such as number of patients, age, gender rate, prior chemotherapy history and ECOG (Eastern Cooperative Oncology Group) performance status (PS). Before performing the analyses, data of each published study were carefully double-checked by another reviewer (M.K.), and any disagreements were resolved by discussion. Whenever possible, we tried to obtain the updated results from the researchers via email, particularly for trials published only in abstract form.

Statistical analysis. The primary outcome measure was OS, which was defined as time from random assignment to death. Secondary outcome measures were PFS, defined as the time between date of random assignment and date of progression, or date of death for patients dead without progression, or last date of follow-up for censored patients; ORR, defined as the sum of partial and complete response rates; and toxicity, which was graded according to NCI Common Toxicity Criteria (CTC).14,19 or on the basis of the Common Terminology Criteria for Adverse Events (CTCAE).21

A hazard ratio (HR) was calculated to assess the survival advantage of the S-1-based chemotherapy as compared with the 5-Fu-based chemotherapy. Odds ratios (ORs) were calculated to assess objective response rate and toxic events. For toxic events, not all publications reported all grades adverse events, so severe (grade 3–4) adverse events data was extracted.

Between-study heterogeneity was estimated using the \( \chi^2 \)-based Q statistic.22 Heterogeneity was considered statistically significant when \( P_{\text{heterogeneity}} \leq 0.1 \) or \( I^2 >50\% \). Primary analyses were done with a fixed effects model; secondary confirmatory analyses were done with a random effects model if there was significant heterogeneity. The presence of publication bias was evaluated by using the Beggs’s and Egger’s tests.23,24

All statistical analyses were conducted with STATA version 10.0 software (Stata Corporation, College Station, TX, USA). A statistical test with a \( P \)-value < 0.05 was considered significant. All \( P \)-values were two-sided. All CIs had a two-sided probability coverage of 95%.

Subgroup analyses were done to establish whether therapeutic efficacy was affected by histological type, prior chemotherapy history and combinations with or without platinum.

Results

Characteristics of included trials. Eight eligible trials14–19,25,26 were identified, including four trials for mCRC and four trials for AGC. The flow diagram is shown in Figure 1. The analysis was conducted on the data of 2182 patients and randomly assigned to receive chemotherapy with S-1 or with 5-Fu, respectively. Of the eight trials, five trials were conducted in Japan,15,17,19,25,26 and three in China.14,16,18 The characteristics of the eight included trials are summarized in Table 1. More than 66.9% of patients have no history of chemotherapy. At the time of analysis, four trials were fully published journal articles,14,19,21,25 while the rest of the trials were published only in abstract form. Finally, all trials used doublet or triplet combination chemotherapy except the Japan Clinical Oncology Group (JOCG) 9912 study19 that used S-1 as the single agent.

Efficacy. Data on OS were available for four trials (1235 patients; Table 2). S-1-based chemotherapy was associated with a statistically significant 13% reduction in the hazard for death as compared with 5-Fu-based chemotherapy (HR, 0.87; 95% CI, 0.77–1.00; \( P = 0.043 \); Fig. 2). Data on PFS were available for five trials (1739 patients; Table 2). S-1-based chemotherapy was also associated with a clinically 13% reduction in the hazard for death as compared with 5-Fu-based chemotherapy, but this difference was not significant (HR, 0.87; 95% CI, 0.72–1.06; \( P = 0.160 \); Fig. 3). Response rate was stated in seven trials, which included 2077 patients (Table 2). S-1-based regimens was characterized by a significant 72% increase in the OR for response in comparison with 5-Fu-based chemotherapy (OR, 1.72; 95% CI, 1.09–2.70; \( P = 0.019 \); Fig. 4).

There was no statistically significant heterogeneity in the HR for OS from the trials, and a fixed-effects model was used. Nevertheless, there was statistically significant heterogeneity both in the HR for PFS and the OR for ORR, so random-effects models were undertaken (Table 2).

Toxicity. A summary of grade 3–4 adverse effects are reported in Table 3. More than 10% of the total patients suffered neutropenia, leucopenia, anemia, or anorexia, but no
significant difference of each adverse event was observed between S-1-based and 5-Fu-based chemotherapy. In contrast, S-1-based chemotherapy was characterized by a significantly higher incidence of diarrhea, fatigue or thrombocytopenia (OR: 3.18, 2.67, 2.30, respectively), and a lower incidence of nausea (OR: 0.69). Nevertheless, the incidence of each mentioned significant adverse effect was much lower than 10%. In addition, no significant difference was observed with regard to treatment-related death. Heterogeneity existed for some adverse events among studies, possibly due to the different combinations and doses used.

Subgroup analysis. Subgroup analyses, which were based on tumor type (mCRC vs AGC), prior chemotherapy history (with no prior chemotherapy history vs with prior chemotherapy history or not clear), and combinations (with vs without platinum), were performed for OS, PFS and ORR (Table 2). The results showed that, non-platinum containing regimens resulted in a modest but significant OS benefit (HR, 0.86; 95% CI, 0.75–0.99; \( P = 0.041 \)) and a 115% increase in ORR (OR, 2.15; 95% CI, 1.16–4.00; \( P = 0.016 \)) in favor of S-1-based regimens. Moreover, S-1-based regimens also significantly improved OS (HR, 0.82; 95% CI, 0.69–0.99; \( P = 0.034 \)) and ORR (OR, 2.20; 95% CI, 1.06–4.55; \( P = 0.034 \)) in patients with no prior chemotherapy. In the subgroup of patients with AGC, statistically significant improvements of PFS (HR, 0.73; 95% CI, 0.62–0.86; \( P < 0.001 \)) and ORR (OR, 2.31; 95% CI, 1.29–4.13; \( P = 0.005 \)) were observed in the S-1-based regimens.

Publication bias. We performed Begg’s funnel plot and Egger’s test to assess the publication bias of literature. The shapes of the funnel plots (Figures not shown) indicated the absence of publication bias. Furthermore, Egger’s test was used to statistically confirm the funnel plot symmetry (\( P = 0.814 \) for OS, \( P = 0.554 \) for PFS). The results still did not suggest any evidence of publication bias.

Discussion

Fig. 1. Trials flow diagram.

The final results of this meta-analysis showed that S-1-based chemotherapy significantly improved OS in comparison with 5-Fu-based chemotherapy. Our data on ORR reinforces further the survival result because there was a higher response rate in the S-1 arm than that in the 5-Fu arm. However, meta-analysis showed that S-1-based therapy was not better than 5-Fu-based therapy with respect to PFS. With regard to safety profile, there was no significant difference between the two groups with respect to all grade 3–4 adverse events except for diarrhea, fatigue thrombocytopenia and nausea. However, the four mentioned adverse events appeared uncommonly in both arms. Accordingly, S-1-based therapy was associated with longer OS and higher response rate and almost equivalent safety compared with 5-Fu-based therapy.

Four of the eight trials provided data on OS (Table 2). \( (15,17–19) \) The results in all four trials showed that S-1-based chemotherapy did not prolong OS of patients with GI cancer. Regardless of there being no significant difference on OS in each trial, the median OS in patients assigned S-1 was much longer than that in patients assigned 5-Fu in all trials except the Xu et al. trial (Table 1). Meanwhile, the forest plot of OS (Fig. 2) showed favorable results for S-1 compared with 5-Fu for all included trials except the same trial. All the trials indicated the potential benefit of S-1 except the Xu et al. trial. Xu reported that median OS was 10.00 months (95% CI, 8.59–14.52) in the S-1 group compared with 10.46 months (95% CI, 8.92–13.84) in the 5-Fu group (HR, 1.05; 95% CI, 0.71–1.54). In spite of this, statistically significant difference in OS in favor of S-1 was still observed in this meta-analysis, and in view of the convenience of an oral administration, S-1 could be considered to replace 5-Fu for treatment of AGC or mCRC.

Seven trials provided data on response rate directly or indirectly (Table 2). \( (14–16,18,19,25,26) \) All of the trials reported that the response rate in the S-1 group was higher than that in the 5-Fu group except the SOFT study \( (25) \) (62% vs 63% in each group). The overall response rates were 38.6% in the S-1 arm and 30.5% in the 5-Fu arm in this analysis, which demonstrated a 72% increase in the OR for response in the S-1 arm than that in the 5-Fu arm, and the difference was significant (\( P = 0.019 \)).
| Author, year | Country | Type | Phase | Line | Treatment regimen | Number | Male (%) | Median age (years) | Median OS (months) | Median PFS (months) | CR+PR (%) | ECOG PS | Jadad score |
|-------------|---------|------|-------|------|-------------------|--------|----------|-------------------|-------------------|-------------------|------------|---------|-----------|
| Andoh et al. 2011 | Japan | mCRC | — | — | S-1/CPT-11/BV | 30 | — | — | 11.5 | — | 72.0 | — | 1 |
| Otsuji et al. 2012 | Japan | mCRC | II | 1st | S-1/LV/L-OHP | 56 | — | — | 28.5 | 9.6 | — | 0–1 | 2 |
| Baba et al. 2011 | Japan | mCRC | II | 2nd | S-1/CPT-11 | 49 | — | — | 25.9 | 6.9 | — | — | — |
| Yamada et al. 2013 | Japan | mCRC | III | 1st | S-1/L-OHP/BV | 255 | 56.0 | 63.0 | 29.6 | 11.7 | 62.0 | 0–1 | 3† |
| Xu et al. 2013 | China | AGC | III | — | S-1/DDP | 120 | — | — | 10.0 | — | — | 22.5 | — | 1 |
| Jin et al. 2008 | China | AGC | III | 1st | S-1/DDP | 74 | — | 56.5 | — | — | 37.8 | — | 1 |
| Boku et al. 2009 | Japan | AGC | III | 1st | S-1 | 234 | 74.8 | 64.0 | 11.4 | 4.2 | 28.0 | 0–2‡ | 3† |
| Huang et al. 2013 | China | AGC | III | 1st | S-1/paclitaxel | 119 | 74.8 | 56.0 | — | 5.1 | 42.0 | — | 2† |

AGC, advanced gastric cancer; BV, bevacizumab; CPT-11, irinotecan; DDP, cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; L-OHP, oxaliplatin; LV, leucovorin; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival. —, not reported; †full published; ‡Only three persons had an ECOG performance status of two in each group, all the other individuals had an ECOG performance status of 0 or 1.

Table 2. Hazard ratios, P-value, and heterogeneity for progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) in the stratified analyses

| Efficacy | OS | PFS | ORR |
|----------|----|-----|-----|
|          | n | HR  | P | P< sub>H sub> | I^2/% | HW | n | HR  | P | P< sub>H sub> | I^2/% | HW | n | OR  | P | P< sub>H sub> | I^2/% | HW |
| All      | 4 | 0.87 (0.77, 1.00) | 0.043 | 0.687 | 0.0 | 100 | 5 | 0.87 (0.72, 1.06) | 0.160 | 0.016 | 67.4 | 100 | 7 | 1.72 (1.09, 2.70) | 0.019 | 0.001 | 73.7 | 100 |
| Type     | mCRC | 2 | 0.88 (0.72, 1.07) | 0.206 | 0.562 | 0.0 | 43.2 | 3 | 1.03 (0.91, 1.18) | 0.635 | 0.695 | 57.6 | 0.0 | 3 | 1.05 (0.78, 1.42) | 0.736 | 0.663 | 0.0 | 42.3 |
|          | AGC | 2 | 0.87 (0.73, 1.03) | 0.113 | 0.287 | 11.9 | 56.8 | 2 | 0.73 (0.62, 0.86) | <0.001 | 0.313 | 1.6 | 42.4 | 4 | 2.31 (1.29, 4.13) | 0.005 | 0.020 | 69.5 | 57.7 |
|          | PCH | No | 2 | 0.82 (0.69, 0.99) | 0.034 | 0.761 | 0.0 | 51.4 | 4 | 0.82 (0.65, 1.02) | 0.079 | 0.037 | 64.7 | 76.0 | 4 | 2.20 (1.06, 4.55) | 0.034 | <0.001 | 84.7 | 60.8 |
|          | Yes/not clear | 2 | 0.93 (0.77, 1.13) | 0.471 | 0.497 | 0.0 | 48.6 | 1 | 1.06 (0.87, 1.29) | 0.0 | 0.0 | 24.0 | 3 | 1.16 (0.79, 1.70) | 0.459 | 0.826 | 0.0 | 39.2 |
|          | Platinum | With | 2 | 0.94 (0.69, 1.29) | 0.696 | 0.337 | 0.0 | 17.2 | 2 | 1.01 (0.84, 1.21) | 0.899 | 0.430 | 0.0 | 33.6 | 3 | 1.28 (0.75, 2.19) | 0.363 | 0.069 | 62.5 | 45.8 |
|          | | Without | 2 | 0.86 (0.75, 0.99) | 0.041 | 0.576 | 0.0 | 82.8 | 3 | 0.82 (0.62, 1.08) | 0.153 | 0.010 | 78.1 | 66.4 | 4 | 2.15 (1.16, 4.00) | 0.016 | 0.020 | 69.6 | 54.2 |

AGC, advanced gastric cancer; HR, hazard ratio; mCRC, metastatic colorectal cancer; PCH, prior chemotherapy history; P<sub>H</sub>, heterogeneity P. —, cannot be calculated.
Data on PFS were available in five trials, and no significant difference was observed on PFS in our meta-analysis (Table 2). However, two of the five trials, which investigated the benefit of S-1 in AGC patients, both demonstrated a significant difference in favor of S-1-based therapy. Subgroup analysis based on tumor type confirmed the significant improvement on PFS in AGC patients with S-1-based regimens. The PFS benefit of S-1 should be further investigated in more trials.

In addition, the following issues may confound the assessment of survival and response rate and are worthy of further discussion. First, the inconsistency of systemic therapy before and after the study among the eight trials may affect the end points. Subgroup analysis based on prior chemotherapy history indicated that S-1-based therapy could prolong OS and increase ORR of patients with no history of prior chemotherapy in comparison with 5-Fu-based therapy. Second, platinum is toxic and is not well-tolerated for some patients, which may also potentially affect the results. In the subgroup of non-platinum containing regimens, OS and ORR were significantly improved in the S-1-based-therapy. Third, tumor type may be the influencing factor. As for AGC patients, S-1-based regimens were associated with statistically significant improvements of PFS and ORR in comparison with 5-Fu-based regimens.

The findings of our study showed that almost equivalent tolerance was observed between the two groups except for significant increases in grade 3–4 diarrhea, fatigue, thrombocytopenia and a decrease in grade 3–4 nausea in S-1-based group. However, these mentioned significant adverse effects were reported in a few patients in each group, and the incidence of each adverse event was much lower than 10% (Table 3). All the toxicities were tolerable, predictable, and manageable. As for treatment-related death, which was an important toxic indicator, was reported only in four trials. The difference on treatment-related death was not statistically significant in this meta-analysis.

The pharmacokinetic data demonstrated that the appropriate dose of S-1 is dependent on ethnic differences as well as differences in toxicity profile. The FLAGS trial has been the only non-Asian trial that compared S-1 with 5-Fu in advanced GI cancer until now, and the dose of S-1 was lower than that in these included Asian trials. This trial showed that cisplatin/S-1 did not prolong OS of patients with advanced gastric cancers compared with cisplatin/5-Fu, but it did result in a significantly improved safety profile. With these differences, our results in this meta-analysis cannot be simply extrapolated to Western patients. And the survival benefits of S-1-based therapy should be further investigated in European and North American populations in the near future.

The limitations of these studies also need attention. First, as we all know, the results of any meta-analysis were affected by

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**Fig. 2.** Fixed-effects model of hazard ratio (95% CI) of overall survival (OS) associated with S-1-based therapy compared with 5-Fu-based therapy.

**Fig. 3.** Random-effects model of hazard ratio (95% CI) of progression-free survival (PFS) associated with S-1-based therapy compared with 5-Fu-based therapy.

**Fig. 4.** Random-effects model of hazard ratio (95% CI) of overall response rate (ORR) associated with S-1-based therapy compared with 5-Fu-based therapy.
the quality of the individual studies. All of the trials were RCTs, while four of them were published only in abstract form, and an insufficient amount of data might potentially limit detection of S-1-based therapy effects. Furthermore, no updated or confirmed results could be obtained from the authors. Therefore, our results should be interpreted with care. Second, our meta-analysis was based on abstracted data and not on individual patient data (IPD). Meta-analyses based on IPD tend to give a more robust estimation for the association compared with published data analyses. Third, the difference in treatment schedules among the trials (data not shown) might contribute to increase the clinical heterogeneity of the meta-analysis. Fourth, the line of therapy was inconsistent among the eight trials that might confound the assessment of OS if the drugs of its use differed before or after the study. Finally, lack of blinding, which could be inevitable in all these included studies, might have resulted in an overestimate of the effects. Because the two treatment methods studied were quite different (tablet vs injection), the treatment allocation could not be masked from the investigators or patients.

Combination therapy is now a predominant approach in cancer chemotherapy. Most recent combination studies of S-1 with cisplatin, irinotecan, and oxaliplatin and other anticancer agents indicate the crucial importance of understanding the combination between the best partner drug and S-1. While, S-1 plus molecular-targeted agents are promising. Furthermore, some experts reported that “S-1 and low-dose CDDP therapy” and “alternate-day S-1 regimen” might be considered as the most patient-friendly therapies available to date.

In summary, S-1-based chemotherapy was not only superior to 5-Fu-based chemotherapy in terms of OS, but also lead to increased responses, especially in subgroups of patients with no history of prior chemotherapy and with non-platinum containing regimens. Although non-significant difference on PFS between the two arms was obtained in this meta-analysis, significant PFS and ORR benefits of S-1 in comparison with 5-Fu were indicated in the subgroup of AGC patients. All of these results confirmed that oral S-1 could replace infusional 5-Fu in the treatment of advanced GI cancer with almost equivalent tolerance and much more convenience. The superiority of S-1 to 5-Fu needed to be further evaluated and confirmed through larger studies with longer observation periods in both Asian and Western countries.

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