

S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer: A meta-analysis

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Received: February 26, 2014 Revised: April 24, 2014

Accepted: May 25, 2014

Published online: September 7, 2014

Abstract

AIM: To assess the efficacy and tolerability of S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer (AGC).

METHODS: We extracted reported endpoints, including overall survival (OS), progression-free survival (PFS), time-to-treatment failure (TTF), objective response rate (ORR) and adverse effects, from randomized controlled trials identified in PubMed, the Cochrane library, Science Direct, EMBASE and American Society of Clinical Oncology meetings. Stata software was used to calculate the pooled values.

RESULTS: Seven randomized controlled trials involving 2176 patients were included in this meta-analysis. Compared to non-S-1-based regimens, the use of S-1-based regimens were associated with an increase in ORR (RR = 1.300; 95%CI: 1.028-1.645); OS (HR = 0.89; 95%CI: 0.81-0.99; $P = 0.025$), TTF (HR = 0.83; 95%CI: 0.75-0.92; $P = 0.000$), and a lower risk of febrile neutropenia (RR = 0.225; $P = 0.000$) and stomatitis (RR = 0.230; $P = 0.032$). OS, PFS and TTF

were prolonged, especially in the Asian population. In subgroup analysis, statistically significant increases in ORR (RR = 1.454; $P = 0.029$), OS (HR = 0.895; $P = 0.041$) and TTF (HR = 0.832; $P = 0.000$) were found when S-1-based chemotherapy was compared to 5-fluorouracil (5-FU)-based chemotherapy. The incidence of leukopenia (RR = 0.584; $P = 0.002$) and stomatitis (RR = 0.230; $P = 0.032$) was higher in the 5-FU-based arm. S-1-based regimens had no advantage in ORR, OS, PFS, TTF and grade 3 or 4 adverse events over capecitabine-based regimens.

CONCLUSION: S-1-based chemotherapy may be a good choice for AGC because of longer survival times, better tolerance and more convenient use.

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Key words: S-1; Advanced gastric cancer; Chemotherapy; First line treatment; Meta-analysis

Core tip: This meta-analysis aimed to assess the efficacy and tolerability of S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer (AGC). Compared to non-S-1-based regimens, the use of S-1-based regimens were associated with an increase in the objective response rate, overall survival, time-to-treatment failure, and a lower risk of grade 3 or 4 adverse events. S-1-based chemotherapy may be a good choice for AGC, at least in Asia because of longer survival times, better tolerance and more convenient use.

Yang J, Zhou Y, Min K, Yao Q, Xu CN. S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer: A meta-analysis. *World J Gastroenterol* 2014; 20(33): 11886-11893 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i33/11886.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i33.11886>

INTRODUCTION

Although gastric cancer rates have decreased substantially in most parts of the world^[1] because of advances in early diagnosis, control of chronic *Helicobacter pylori* infection and changes in lifestyles, it remains a common and devastating disease. A total of 989600 new gastric cancer cases and 738000 deaths are estimated to have occurred in 2008, accounting for 8% of the total cases and 10% of total deaths^[2]. Nowadays, surgery remains the primary treatment, with an average 5-year survival rate of 20%-30%. More than two-thirds of patients have unresectable disease when diagnosed^[3], so chemotherapy is regarded as a significant and basic treatment method. Compared with the best supportive care, chemotherapy increases the 1-year survival rate and provides a longer symptom-free period of 6 mo and an improvement in quality of life^[4,5]. Many studies based on combinations of new-generation agents, like S-1, capecitabine, taxanes, oxaliplatin and irinotecan have been undertaken^[5-8], and new and more effective regimens are being explored.

S-1 is a novel oral derivative of 5-FU, and contains tegafur/gimeracil/oteracil potassium in a molar ratio of 1.0:0.4:1.0. Tegafur (FT) is a depot form of fluorouracil, which releases 5-fluorouracil (5-FU) slowly in the body^[9]. Gimeracil, a dihydropyrimidine dehydrogenase inhibitor, contributes to a decrease in 5-FU catabolism and to significantly higher blood levels of 5-FU compared to FT alone^[10,11]. Oteracil potassium (Oxo), another enzyme inhibitor of 5-FU, can suppress the gastrointestinal toxicity of FT^[12]. In theory, S-1 is more tolerable and effective than 5-FU, and will be more convenient to use for patients with advanced gastric cancer (AGC). Based on the encouraging results from a number of phase II trials for S-1-based chemotherapy^[13-19], some randomized controlled trials were carried out to compare S-1-based chemotherapy and non-S-1-based chemotherapy. However, there is controversy and uncertainty about the advantages of S-1^[20-23]. Therefore, we attempted to assess the benefit of S-1-based chemotherapy through an exhaustive meta-analysis from all relevant trials.

MATERIALS AND METHODS

Aims

This meta-analysis systematically reviewed the published literature of randomized controlled trials, comparing the following therapies: S-1-based chemotherapy *vs* non-S-1-based chemotherapy; S-1-based chemotherapy *vs* 5-FU- or capecitabine-based chemotherapy in subgroup analyses.

Search strategy

S-1 and AGC were used as search terms. PubMed, the Cochrane library, Science Direct, EMBASE and American Society of Clinical Oncology meetings were retrieved, with a censor date up to November 2013. The search was limited to English language and human-based papers.

Case-control and retrospective studies were excluded. To ensure that all relevant trials were included, we scanned related literature and references in the selected articles.

Study selection

We checked each article by viewing the title, abstract, and even the full text. Trials were included if they (1) were randomized controlled phase II or phase III trials; and (2) included patients receiving regimens which compared S-1-based regimens with non-S-1-based regimens given as first-line chemotherapy of AGC. We defined "advanced gastric cancer" as unresectable or recurrent or metastatic disease. Trials were excluded if patients also had radiotherapy, immunotherapy, or preoperative or intraperitoneal chemotherapy. Review articles, case reports, and letters were excluded. All different opinions were discussed. Complete articles of pertinent literature were used in this meta-analysis.

Data extraction

Author name, year of publication, chemotherapy regimens, objective response rate (ORR), prognosis and adverse events in eligible trials were extracted. The ORR was the percentage of patients who had a complete or partial tumor response. Time-related endpoints [overall survival (OS), progression-free survival (PFS) and time-to-treatment failure (TTF)] were used to measure prognosis. OS was defined as the time from random assignment to date of death from any cause. PFS was calculated from the date of randomization to the date of disease progression or death from any cause. TTF included progression, death or withdrawal. If necessary, we did a simple calculation to transform initial data into the forms suitable for meta-analysis. Likewise, data extraction was performed independently by two reviewers.

Statistical analysis

Time-to-event data (OS, PFS and TTF) were summarized using HR and 95% CIs. Dichotomous data (ORR and adverse events) were summarized using relative risks (RR) and 95% CIs. Stata software (version 12.0; Stata Corp LP, College Station, TX, United States) was used to calculate the pooled values.

Heterogeneity between studies was tested using χ^2 statistics and measured with the *P* value and *I*² statistic. *I*² lay between 0% and 100%, and a value of 0% indicated no observed heterogeneity, with larger values indicating increasing heterogeneity. The DerSimonian-Laird method (random-effects model) was used if heterogeneity existed and could not be explained or corrected. Otherwise, the Mantel-Haenszel method (fixed-effects model) was used. In the absence of heterogeneity, the fixed-effects and random-effects models provide similar results.

Forest plots were used to depict HRs and RRs within individual trials and overall. Begg's funnel plots were used to assess the potential publication bias by Egger's linear regression test. All *P*-values were two-sided at the 5% level, and CIs had two-sided probability coverage of 95%.

Table 1 Baseline characteristics

| Study | Year | Country | Number of patients | | Treatments | |
|--|------|-----------|--------------------|---------|---|--|
| | | | S-1 | non-S-1 | Experimental arm | Control arm |
| Ajani <i>et al</i> ^[24] | 2013 | Non-Asian | 521 | 508 | S-1: 25 mg/m ² , B.i.d, day 1-21; cisplatin: 75 mg/m ² , <i>civ</i> 1-3 h, day 1, q.4.w. | 5-FU: 1000 mg/m ² /24 h, day 1-5; cisplatin: 100 mg/m ² , <i>civ</i> 1-3 h, q.4.w. |
| Huang <i>et al</i> ^[25] | 2013 | China | 119 | 110 | S-1: 80-120 mg/d, day 1-14; paclitaxel: 60 mg/m ² , <i>iv</i> , day 1, 8 and 15, q.4.w. | 5-FU: 500 mg/m ² , <i>civ</i> , day 1-5; leucovorin 20 mg/m ² , <i>iv</i> , day 1-5; paclitaxel: 60 mg/m ² , <i>iv</i> , day 1, 8 and 15, q.4.w. |
| Kim <i>et al</i> ^[26] | 2012 | Korea | 65 | 64 | S-1: 80 mg/d, day 1-14; Oxaliplatin: 130 mg/m ² , <i>iv</i> (2 h), day 1, q.3.w. | Capecitabine: 2000 mg/d, day 1-14; Oxaliplatin: 130 mg/m ² , <i>iv</i> (2 h), day 1, q.3.w. |
| Nishikawa <i>et al</i> ^[27] | 2012 | Japan | 80 | 77 | (sequential), S-1: 80 mg/m ² , day 1-28, 2-wk rest followed by PTX; or (concurrent), S-1: 14 d and PTX: 50 mg/m ² , day 1, 8, q.3.w. | (sequential), intravenous 5-FU: 800 mg/m ² , <i>iv</i> , day 1-5, followed by weekly PTX at 80 mg/m ² ; or (concurrent), 5-FU: 600 mg/m ² , <i>iv</i> , day 1-5 and weekly PTX at 80 mg/m ² , q.4.w. |
| Jeung <i>et al</i> ^[20] | 2010 | Korea | 37 | 38 | S-1: 35 mg/m ² , B.i.d, day 1-14; doc: 35 mg/m ² , day 1, 8, q.3.w. | cisplatin: 35 mg/m ² , day 1, 8; doc: 35 mg/m ² , day 1, 8, q.3.w. |
| Boku <i>et al</i> ^[22] | 2009 | Japan | 234 | 232 | S-1: 40 mg/m ² , B.i.d, day 1-28, q.6.w. | 5-FU: 800 mg/m ² , <i>civ</i> , day 1-5, q.4.w. |
| Lee <i>et al</i> ^[23] | 2008 | Korea | 45 | 46 | S-1: 40 mg/m ² (BSA < 1.25 m ²), 50 mg/m ² (BSA: 1.25-1.5 m ²), 60 mg/m ² (BSA > 1.5 m ²), B.i.d, day 1-28, q.6.w. | Capecitabine: 1250 mg/m ² , B.i.d, day 1-14, q.3.w. |

5-FU: 5-fluorouracil; PTX: Paclitaxel; BSA: Body surface area.

RESULTS

Seven randomized controlled trials involving 2176 patients met the inclusion criteria and were included in this meta-analysis^[20,22-27]. All the trials assessed adverse events according to the National Cancer Institute's common toxicity criteria. The details of the articles were summarized in Table 1.

S-1-based vs non-S-1-based chemotherapy

The HR summarizes survival for S-1-based compared with non-S-1-based chemotherapy, with an HR less than 1 indicating a survival advantage for S-1-based chemotherapy.

Compared to non-S-1-based regimens, the use of S-1-based regimens was associated with an increased ORR (RR = 1.300; 95%CI: 1.028-1.645). S-1-based chemotherapy had a marginal overall survival benefit compared to the control group (Figure 1), with a HR of 0.89 (95%CI: 0.81-0.99; $P = 0.025$). There was no significant heterogeneity between the studies ($P = 0.263$; $I^2 = 22.7\%$). The PFS was not significantly better in the S-1-based group (HR = 0.84; 95%CI: 0.70-1.00; $P = 0.052$) (Figure 2), but TTF was significantly in favor of the S-1-based group (Figure 3), with a pooled HR of 0.83 from three related articles (95%CI: 0.75-0.92; $P = 0.00$). There was no significant inter-trial heterogeneity for the endpoints of TTF ($P = 0.094$; $I^2 = 57.6\%$).

Six trials assessed adverse effects. Most grade 3 or 4 hematological and nonhematologic toxicities were not reduced in the S-1-based group. Only the risk of febrile neutropenia (RR = 0.225; 95%CI: 0.126-0.515; $P = 0.00$) and stomatitis (RR = 0.230; 95%CI: 0.060-0.878; $P = 0.032$) were lower with S-1-based chemotherapy than non-S-1-based chemotherapy. The details are listed in Table 2.

Only one of the trials, by Ajani *et al*^[21], was from non-Asian countries. So we pooled the data from Asian countries, and found a longer OS (HR = 0.87; 95%CI: 0.75-0.99; $P = 0.048$), PFS (HR = 0.78; 95%CI: 0.68-0.89; $P = 0.00$) and TTF (HR = 0.76; 95%CI: 0.64-0.91; $P = 0.003$) in the S-1-based group. Only grade 3 or 4 leukopenia was less in the non-S-1-based chemotherapy (RR = 2.198; 95%CI: 1.403-3.443; $P = 0.001$).

S-1-based vs 5-FU-based or capecitabine-based chemotherapy

There were three standalone randomized controlled trials comparing S-1-based and 5-FU-based chemotherapy. Two trials assessed whether there were benefits of S-1-based vs capecitabine-based chemotherapy. In a subgroup analysis a pooled HR < 1 represents superiority of S-1-based chemotherapy. S-1-based chemotherapy increased ORR (RR = 1.454; 95%CI: 1.038-2.036; $P = 0.029$), and prolonged the OS and TTF compared with 5-FU-based chemotherapy, with HR of 0.895 and 0.832, respectively. However, no significant difference in PFS between the two groups was observed (HR = 0.809; $P = 0.086$). Also, S-1 had no advantage in ORR, OS, PFS and TTF over capecitabine (Table 3).

The incidence of leukopenia (RR = 0.584; $P = 0.002$) and stomatitis (RR = 0.230; $P = 0.032$) appeared to be higher in the 5-FU-based arm. The other grade 3 or 4 hematological and nonhematologic toxicities were not less in the S-1-based group. The frequency of these grade 3 or 4 adverse events did not differ between S-1-based and capecitabine-based chemotherapy. The details are listed in Table 4.

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias. Studies were plotted in order of

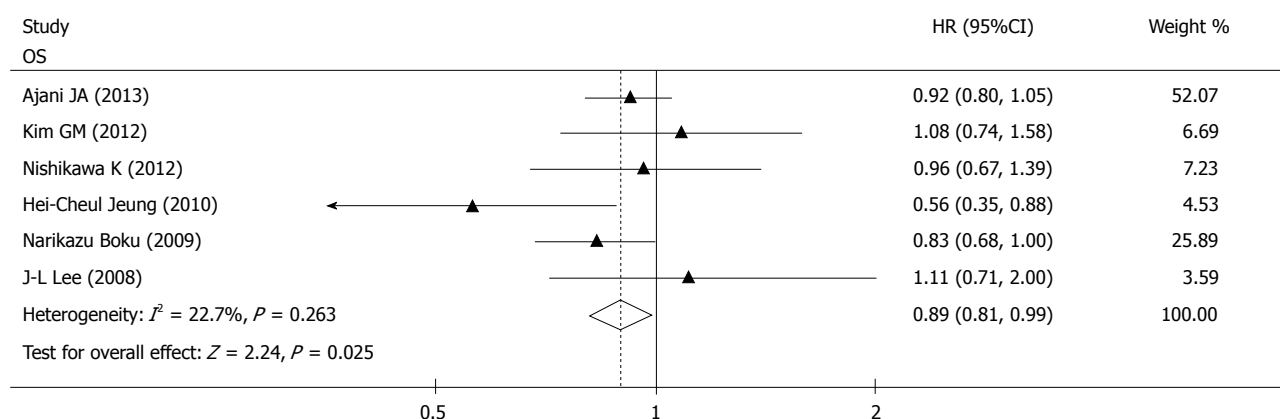


Figure 1 Comparison of overall survival between S-1-based chemotherapy and non-S-1-based chemotherapy. Values less than 1 indicate a survival advantage for S-1-based chemotherapy. OS: Overall survival; HR: Hazard ratio.

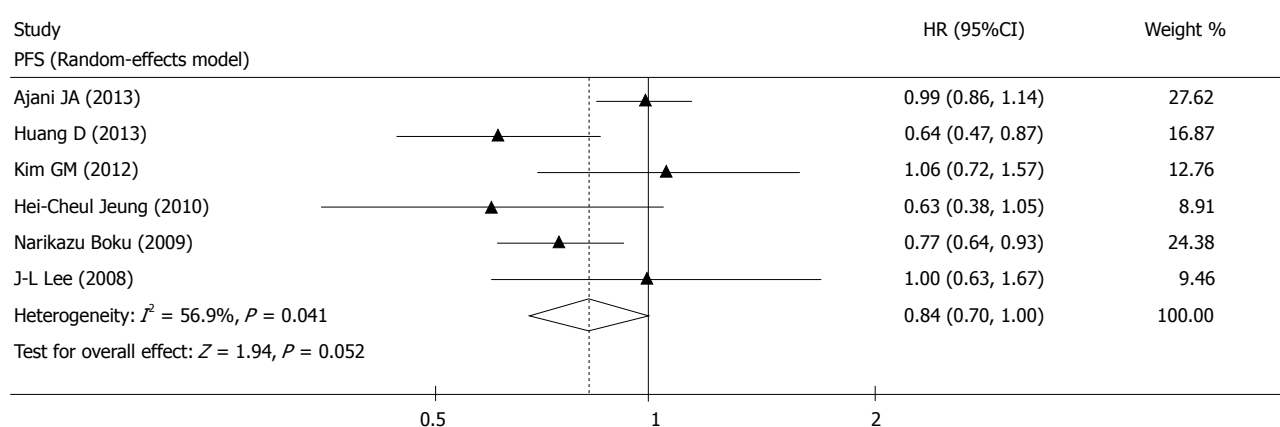


Figure 2 Comparison of progression-free survival between S-1-based chemotherapy and non-S-1-based chemotherapy. Values less than 1 indicate a survival advantage for S-1 based chemotherapy. PFS: Progression-free survival; HR: Hazard ratio.

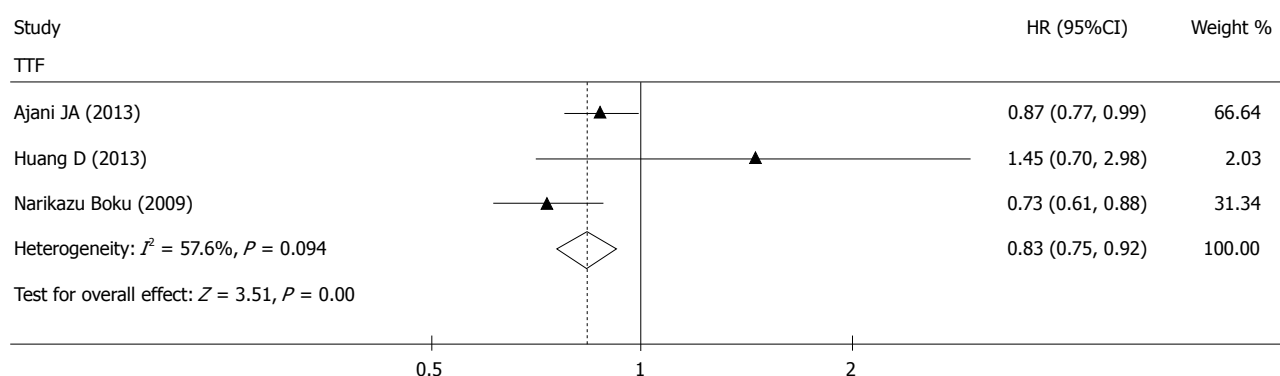


Figure 3 Comparison of time-to-treatment failure between S-1-based chemotherapy and non-S-1-based chemotherapy. Values less than 1 indicate a survival advantage for S-1-based chemotherapy. TTF: Time-to-treatment failure; HR: Hazard ratio.

decreasing variance of log HR. No publication bias was detected for all comparisons. Begg's funnel plots for the comparison of OS (Egger's test: $P = 0.921$; Begg's test: $P = 0.851$) are shown in Figure 4.

DISCUSSION

No standard chemotherapeutic regimens for AGC have

been established worldwide as yet. Longer survival time, fewer adverse effects, better compliance and higher quality of life are sought. S-1, one kind of oral 5-FU, which offers convenience and tolerance for patients compared with traditional chemotherapy, may be an appropriate choice. Since S-1 was first approved by New Drug Application (NDA) in 1997 for chemotherapy of gastric cancer, numerous phase II clinical trials and retrospective

Table 2 Comparison of toxicity between S-1-based chemotherapy and non-S-1-based chemotherapy

| Toxicity | Number of Trials | Incidence of toxicity (%) | | RR (95%CI) | P value |
|-----------------------------------|------------------|---------------------------|-------------|---------------------|---------|
| | | S-1 Arm | Non-S-1 Arm | | |
| Hematologic | | | | | |
| Anemia | 6 | 14.01 | 14.86 | 1.150 (0.720-1.837) | 0.560 |
| Neutropenia | 6 | 17.54 | 24.80 | 1.043 (0.451-2.413) | 0.922 |
| Thrombocytopenia | 4 | 3.91 | 5.22 | 0.736 (0.499-1.085) | 0.121 |
| Leukopenia | 6 | 8.87 | 9.15 | 1.334 (0.524-3.397) | 0.546 |
| Febrile neutropenia | 3 | 0.86 | 3.54 | 0.225 (0.126-0.515) | 0.000 |
| Neutropenic infection | 3 | 0.67 | 0.39 | 1.450 (0.476-4.424) | 0.513 |
| Nonhematologic | | | | | |
| Fatigue | 6 | 8.67 | 8.37 | 1.041 (0.788-1.375) | 0.777 |
| Vomiting | 5 | 4.29 | 5.61 | 0.769 (0.530-1.114) | 0.164 |
| Nausea | 6 | 5.91 | 7.38 | 0.805 (0.583-1.111) | 0.187 |
| Diarrhea | 6 | 5.24 | 3.54 | 1.288 (0.590-2.813) | 0.525 |
| Abdominal pain | 2 | 4.00 | 2.76 | 1.469 (0.925-2.335) | 0.103 |
| Anorexia | 6 | 7.44 | 6.99 | 1.074 (0.790-1.461) | 0.647 |
| Weight decreased | 2 | 2.00 | 3.25 | 0.625 (0.369-1.061) | 0.082 |
| Stomatitis/mucosal inflammation | 4 | 1.53 | 11.81 | 0.230 (0.060-0.878) | 0.032 |
| Liver function | 3 | 0.86 | 0.69 | 1.221 (0.481-3.103) | 0.674 |
| Neuropathy, peripheral | 5 | 0.67 | 0.89 | 0.724 (0.274-1.915) | 0.515 |
| Alopecia | 2 | 0.38 | 0.30 | 1.205 (0.300-4.840) | 0.792 |
| Palmar-plantar erythrodysesthesia | 4 | 0.38 | 0.59 | 0.719 (0.241-2.150) | 0.555 |

RR: Relative risk.

Table 3 Comparison of objective response rate, overall survival, progression-free survival and time-to-treatment failure between S-1-based chemotherapy and 5-FU-based or capecitabine-based chemotherapy

| Subgroups | ORR | | OS | | PFS | | TTF | |
|---------------------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|----------------|
| | RR (95%CI) | P value | HR (95%CI) | P value | HR (95%CI) | P value | HR (95%CI) | P value |
| S-1 vs 5-FU | 1.454 (1.038-2.036) | 0.029 | 0.895 (0.805-0.995) | 0.041 | 0.809 (0.635-1.030) | 0.086 | 0.832 (0.751-0.992) | 0 |
| S-1 vs capecitabine | 0.952 (0.649-1.397) | 0.801 | 1.090 (0.803-1.481) | 0.579 | 1.036 (0.764-1.405) | 0.819 | Not applicable | Not applicable |

ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; TTF: Time-to-treatment failure; 5-FU: 5-fluorouracil.

studies in Japan were started. An ORR of 20%-40%^[28-31] and median OS of 250 to 350 d^[30,32] were obtained for S-1 monotherapy in patients with AGC. The results were encouraging. So S-1 has been widely used in Japan for the treatment of AGC^[33]. Recently, some phase II and phase III clinical randomized controlled trials both in Asian and non-Asian countries, compared S-1-based chemotherapy with non-S-1-based chemotherapy, and produced conflicting results. With limited sample sizes, it was difficult to draw definitive conclusions. A meta-analysis provides supreme evidence and a reliable answer to a clinical question, and this study pooled the data of 2176 patients from seven independent trials with a median follow-up about 2 years. This meta-analysis showed that S-1-based regimens were more effective than non-S-1-based regimens, with an absolute improvement of 11% in OS and 17% in TTF. The pooled HR also showed comparable PFS of the two treatments and slightly favored S-1-based therapy.

There are some limitations and explanations on the results. The impact of first line therapy on OS may be confounded by second-line or third-line therapies. However, follow-up treatments were not extensively reported in most of the eligible trials, so we could not analyze their possible impact on survival. However, follow-up treat-

ments did not markedly alter TTF and PFS, which also confirmed the advantage of S-1-based chemotherapy. Another important factor influencing prognosis was follow-up time. By reviewing the included studies, we found most of the patients had passed away when follow-up ended and it indicated the follow-up was adequate. On the other hand, all the trials enrolled in this meta-analysis used daily administration of S-1, but it was demonstrated that, compared with daily administration, alternate-day administration of S-1 reduced adverse effects and provided sufficient clinical effects^[34]. A retrospective study of alternate-day treatment with S-1 showed a response rate of 25%, with a median survival time of 338 d in patients with AGC^[35]. In a mouse model, alternate-day treatment with S-1 was equivalent to daily treatment in terms of relative inhibition of tumor growth^[36]. We hypothesize that alternate-day administration of S-1 may reduce adverse effects, improve compliance, and thus prolong survival time. Only one of the trials researched by Ajani *et al*^[21] came from non-Asian countries. According to the suggestion of the reviewer, we pooled the data from Asian countries, and found longer OS, PFS and TTF for S-1-based treatment. Up to now, the only non-Asian global phase III trial reported a negative result regarding survival time for S-1-based therapy. So the advantage of S-1 in the

Table 4 Comparison of toxicity between S-1-based chemotherapy and 5-fluorouracil- or capecitabine-based chemotherapy

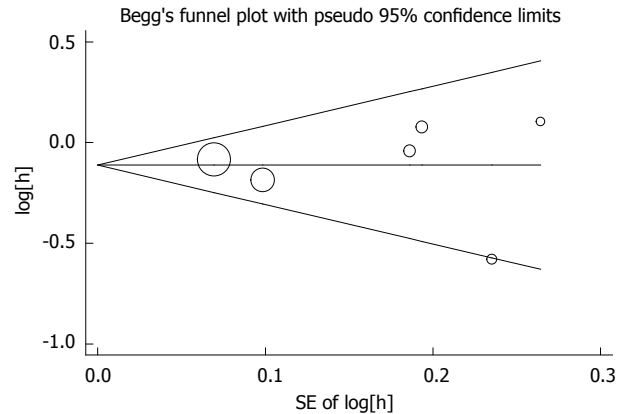
| Toxicity | S-1 vs 5-FU | | S-1 vs capecitabine | |
|-----------------------------------|-------------|---------|---------------------|----------------|
| | RR | P value | RR | P value |
| Hematologic | | | | |
| Anemia | 1.073 | 0.794 | 1.914 | 0.145 |
| Neutropenia | 1.023 | 0.964 | 0.475 | 0.066 |
| Thrombocytopenia | 0.683 | 0.096 | 0.953 | 0.903 |
| Leukopenia | 0.584 | 0.002 | 1.788 | 0.402 |
| Nonhematologic | | | | |
| Fatigue | 1.091 | 0.558 | 0.428 | 0.139 |
| Vomiting | 0.801 | 0.268 | 0.925 | 0.928 |
| Nausea | 0.791 | 0.179 | 1.177 | 0.812 |
| Diarrhea | 1.988 | 0.436 | 0.693 | 0.601 |
| Anorexia | 1.057 | 0.736 | 1.164 | 0.794 |
| Weight decreased | 0.625 | 0.082 | Not applicable | Not applicable |
| Stomatitis/mucosal inflammation | 0.230 | 0.032 | Not applicable | Not applicable |
| Neuropathy, peripheral | 0.808 | 0.722 | Not applicable | Not applicable |
| Palmar-plantar erythrodysesthesia | 1.770 | 0.468 | 0.193 | 0.133 |

5-FU: 5-fluorouracil.

treatment of AGC is especially true in Asian population. The most relevant factor, in our opinion, is that the metabolic rate of conversion of S-1 to 5-FU seems to differ in various ethnic populations. S-1 is converted to 5-FU in the liver mainly by cytochrome P450 2A6 (CYP2A6). There are racial differences in CYP2A6 polymorphisms which affect the clinical outcomes of patients who are undergoing S-1-based chemotherapy for AGC^[37]. Thus we think that the expression of specific genes may finally decide the effectiveness of S-1. For example, Ichikawa *et al.*^[38] found that treatment effects of S-1 monotherapy for gastric cancer are determined by the status of TS gene expression, regardless of DPD gene expression. Ishido *et al.*^[39] proved that intratumoral TS expression was an independent prognostic factor in patients with gastric cancer who received postoperative adjuvant chemotherapy with S-1. The predictive markers of S-1 should be further explored to guide rational clinical therapy.

We also paid close attention to the adverse effects. Most of the toxicities were predictable, tolerable and manageable, and only grade 3 or 4 adverse events were discussed. The use of S-1 did not increase the side effects and even reduced the rate of febrile neutropenia and stomatitis. As we known, S-1 improves the tumor selective toxicity of 5-FU especially by the actions of Oxo^[40], an enzyme inhibitor of 5-FU, which can suppress the gastrointestinal toxicity of FT^[12]. However, in this meta-analysis, we did not find a notable advantage of S-1 regarding gastrointestinal toxicities. The additional effect of concomitant chemotherapeutic agents, such as cisplatin and docetaxel may have affected the results.

Until now, 5-FU has comprised the backbone of chemotherapy for AGC. Oral fluoropyrimidines, such as S-1 and capecitabine, have opened new perspectives for the

**Figure 4 Begg's funnel plot of publication bias.**

treatment of AGC with their simplicity and convenience over traditional 5-FU. So we evaluated their efficacy and safety to provide necessary and important information for clinical decision-making. Finally, S-1-based chemotherapy prolonged OS by 10% and TTF by 17% compared with 5-FU-based chemotherapy, and induced less leukopenia and stomatitis. We also found equivalent ORR, OS, PFS, TTF and grade 3 or 4 hematological and non-hematological toxicities in S-1-based and capecitabine-based chemotherapy. The new generation fluoropyrimidines, like S-1, may be a better choice than 5-FU in clinical use. Also, as they have similar antitumor efficacy and safety, we recommend that S-1 and capecitabine can be used for AGC interchangeably.

In our study, some limitations should be discussed. First, as with any meta-analysis, the study was not based on individual patient data and insufficient original data might limit the outcomes and cause confounding bias. We did our utmost to cover most reported endpoints in the randomized controlled trials and provide robust estimates. Second, heterogeneity between studies was present in this article, with a *P*-value < 0.05, especially in the evaluation of adverse effects. This was related to insufficient sample size and a shortage of some original data. We adjusted for this by using a trim-and-fill method in the random-effects model to make our outcomes statistically credible. Third, the numbers of published studies were not sufficiently large for a comprehensive analysis, particularly for the subgroup analysis, such as irinotecan- or paclitaxel-based regimens *vs* S-1-based regimens. Fourth, no trial showed the correlations between *H. pylori*-positive, Her2+, diffuse type or intestinal type, and the therapeutic effect of S-1, so we did not analyze these aspects in this article.

In conclusion, S-1-based chemotherapy may achieve the goal of longer survival and better tolerability than non-S-1-based chemotherapy as first line treatment for AGC. S-1 is an oral formulation and it is convenient for patients. We believe that S-1 plays an important role and may be a suitable choice in the therapy of AGC. More large scale randomized controlled trials need to be carried out to confirm the findings.

COMMENTS

Background

Gastric cancer remains the second leading cause of cancer-related death in the world. A standard chemotherapy regimen for advanced gastric cancer (AGC) is lacking. New-generation agents are being explored. S-1 is a novel oral formulation of 5-fluorouracil (5-FU). The efficacy and tolerability of S-1-based chemotherapy should be assessed.

Research frontiers

Based on the encouraging results from a number of phase II trials for S-1-based chemotherapy, several phase II and phase III clinical randomized controlled trials, both in Asian and non-Asian countries, compared S-1-based-chemotherapy and non-S-1-based chemotherapy. However, there is controversy and uncertainty about the advantages of S-1.

Innovations and breakthroughs

This systematic review analyzed seven phase III trials and 2176 AGC patients to compare S-1-based vs non-S-1-based chemotherapy and concluded that the use of S-1 was associated with an advantage in terms of objective response rate (ORR), overall survival (OS), time-to-treatment failure (TTF) and toxicities, especially in Asian populations. Similar results were found when comparing with 5-FU-based therapy. Furthermore, S-1-based regimens had no advantage in ORR, OS, progression-free survival, TTF, and adverse events over capecitabine-based regimens. The evidence might be used for future selection of S-1-based chemotherapy for AGC.

Applications

With longer survival, better tolerability, more convenient use for patients, S-1-based chemotherapy may be a suitable choice in the therapy of AGC.

Peer review

The manuscript provides a valuable meta-analysis result, offering suggestions for the S-1-based chemotherapy as a good choice for AGC. The work is well written and interesting because it focuses attention on a controversial issue in the treatment of AGC. Data selection and statistical method is considered as appropriate.

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P- Reviewer: Orditura M, Park SH, Sakakura C

S- Editor: Ding Y **L- Editor:** Cant MR **E- Editor:** Ma S





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ISSN 1007-9327

