**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 12578**

**Columns: META-ANALYSIS**

**Efﬁcacy of S**-**1 *vs* capecitabine for the treatment of gastric cancer: A meta-analysis**

He AB *et al*. S-1 *vs* capecitabine for gastric cancer

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**Received:** July 15, 2014 **Revised:** September 12, 2014

**Accepted:** October 20, 2014

**Published online:**

**Abstract**

**AIM:** To rationally evaluate the effect of S-1 *vs* capecitabinein gastric cancer.

**METHODS:** MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and China Journal Full Text Database were accessed to collect clinical randomized controlled trials regarding the effect of S-1 *vs* capecitabine for the treatment of gastric cancer patients. Statistical analysis was performed by meta-analysis. Four randomized controlled trials met the inclusion criteria.

**RESULTS:** Compared with capecitabine regimens, the 1-year survival rate in gastric cancer patients was 0.80 (95%CI: 0.52-1.21, *P* = 0.29). The overall response rate of S-1 *vs* capecitabine was 0.94 (95%CI: 0.59-1.51, *P* = 0.93). Compared with capecitabine regimens, the most frequent hematologictoxicities were neutropenia (OR = 0.99, 95%CI: 0.65-1.49, *P* = 0.94) and thrombocytopenia (OR = 0.72, 95%CI: 0.31-1.67, *P* = 0.44). The most frequent non-hematologic toxicities included nausea (OR = 0.85, 95%: CI 0.56-1.28, *P* = 0.43) and hand-foot syndrome (OR = 0.16, 95%CI: 0.10-0.27, *P* < 0.00001).

**CONCLUSION:** The existing studies suggest that S-1 is not more effective than capecitabine in the treatment of gastric cancer patients but exhibits less toxicity with regard to hand-foot syndrome.

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**Key words:** Gastric cancer; S-1; Capecibine; Randomized controlled trails; Meta-analysis

**Core tip:** Systemic chemotherapy have been proved to an important treatment for advanced gastric cancer patients, combination regimen containing 5-ﬂourouracil is most commonly used worldwide. S-1 and capecitabine are both oral fluoropyrimidinecarbamate and have been proved to be effective for gastric cancer patients. This is the first meta-analysis to systematically compare the effects between S-1 and capecitabine against gastric cancer for better understanding the efficacy, safety, and feasibility of these anticancer drugs. It may contribute to the better treatment and quality of life for the patients with advanced gastric cancer.

He AB, Peng XL, Song J, Zhang JX, Dong WG, Luo RF, Tang Y. Efﬁcacy of S-1 *vs* capecitabine for the treatment of gastric cancer: A meta-analysis. *World J Gastroenterol* 2014; In press

**INTRODUCTION**

Gastric cancer is the second leading cause of cancer-related deaths in the world[1]. Although the mortality rates of gastric cancer have declined over the past decades, gastric cancer still has a poor prognosis and remains a major health problem[2]. Surgical resection has been accepted as the gold standard and only possibly curative treatment for patients with early stage gastric cancer[3,4]. However，most symptoms of gastric cancer are nonspecific, and screening strategies are unavailable in many areas: thus most patients with gastric cancer are diagnosed in an incurable stage.

Over the past two decades, multiple therapies, including systemic chemotherapy, have demonstrated efficacy indecreasing the risk of relapse and improving survival and quality of life for the patients with advanced gastric cancer[5,6]. Although there are no single agent and globally accepted standard chemotherapy treatment strategies for gastric cancer, combination regimens containing 5-ﬂourouracil (5-FU) are commonly used worldwide[7-11]. The efﬁcacy of oral capecitabine in gastrointestinal cancers has been investigated in a series of studies[12-17],whereas adjuvant chemotherapy with S-1 is recommended in Japan[18,19].

In this study, we performed a meta-analysis to systematically compare the effects between S-1 and capecitabine against gastric cancer to better understand the efficacy, safety, and feasibility of these anticancer drugs.

**MATERIALS AND METHODS**

***Search strategy***

Randomized trials comparing S-1 with capecitabine regimen (single agent, doublet or triplet) for the treatment against gastric cancer were searched from MEDLINE, EMBASE, the Cochrane Controlled Trials Register and China Journal Full text Database up to 1 Oct 2013. The language was limited to English and Chinese. The keywords used were below: gastric cancer, capecitabine, S-1. Moreover, we also searched the reference lists of pertinent manuscripts in order to identify other potentially relevant articles.

***Criteria for study selection***

The inclusion criteria for selected articles were as follows: (1) all were random control tests; (2) adult studies were selected; (3) the experiments compared S-1 with capecitabine for the treatment of gastric cancer; and (4) full texts were selected. Preclinical studies, reviews and case reports, not in the disease being studied were excluded.

***Data extraction***

Two reviewers selected the papers and evaluated the quality of selected papers, then extracted the data independently. A third person was consulted if there were any disagreements. Data on details pertaining to the patients, number of patients at the start of the study and completed subjects, treatment type, outcomes, adverse effects were extracted.

***Statistical analysis***

Statistical analyses were conducted by using the Review Manager version 5.1 of Cochrane Collaboration. Relative risks (RR) and 95%CI were calculated as summary statistics. The estimate of RRfrom individual studies was calculated. Statistically heterogeneity was assessed by using the *I2* test to quantify heterogeneity across studies. If the results of heterogeneity were significant, the random effects model was used to perform analysis. Or else, the fix effects model was employed. Statistical significance was indicated by a P values less than 0.05.

**RESULTS**

***Characteristics of eligible studies***

A total of 371 papers were initially identiﬁed using the search strategy described above. After a thorough screening of the papers, 4 studies were ultimately selected based on the inclusion/exclusion criteria (Figure 1). All of the 4 papers assessed the 1-year survival rate, and three papers evaluated the overall response rate. The study duration ranged from 0.5 to 39.2 mo. The number of patients in each of the included studies ranged from 81 to 129. Two papers were published in English, and two were published in Chinese. The characteristicsof the selected studies are presented in Tables 1 and 2[20-23]. Two studies used SOX compared with XEOLX in gastric cancer[21,23]. One study compared S-1 alone with capecitabine[22]. One study compared TS with TC in patients with gastric cancer[20].

***Analysis of efficacy***

A total of 382 patients from 4 RCTs were included in the 1-year survival analysis; 190 patients were in the S-1 group, and 192 were in the capecitabine group. The total recurrence rate of gastric cancer was 45.8% in the S-1 group and 50.5% in the capecitabine group. The pooled OR for the four studies was 0.80 (OR = 0.80, 95%CI: 0.52-1.21, *P* = 0.29) (Figure 2), suggesting no statistically significant difference between the S-1 and capecitabine groups. No heterogeneity was observed between the selected studies for the treatment analysis (*I2* = 0%).

A total of 301 randomized patients from 3 RCTs were included in the overall response rate analysis; 149 patients were in the S-1 group, and 152 were in the capecitabine group. A summary of the individual studies and pooled results from the primary analysis of overall response rate are presented in Figure 3. The total overall response rate in the S-1 group was 37.6% and 38.8% in the capecitabine group. The pooled OR for the three studies was 0.94 (OR = 0.94, 95%CI: 0.59-1.51, *P* = 0.93), suggesting no statistically significant difference between the S-1 and capecitabine groups. No heterogeneity was observed between the selected studies with regard to the treatment analysis (*I2* = 0%).

***Analysis of toxicity***

Overall, the toxicities observed in the 4 selected RCTs were tolerable. The most common grade 3-4 hematologictoxicities were neutropenia and thrombocytopenia. The most frequent grade 3 or 4 non-hematologic toxicities included nausea and vomiting. The pooled results suggested no significant difference between two treatment groups (Figures 4 and 5). In addition, hand-foot syndrome at any grade was more frequently noted in the capecitabine group than in the S-1 group (Figure 5).

***Publication bias assessment***

Publication bias was assessed by funnel plot. The funnel plots exhibited symmetry (Figure 6), suggesting no publication bias among the selected studies.

**DISCUSSION**

Treatment of gastric cancer has been a major challenge in the past decades given its high incidence. A large number of patients are diagnosed with advanced or metastatic disease. A wide range of studies determined that combination chemotherapy consisting of fluoropyrimidine prolongs survival in patients with advanced gastric cancer[24-28]. Since then,combination regimes consisting of fluoropyrimidine have made undeniable gains in improving survival rates for patients with advanced gastric cancer. Given the relatively short overall survival of advanced gastric cancer patients and the palliative nature of systemic chemotherapy, chemotherapeutic agents should be selected based on efficacy, low toxicity and convenient administration.

S-1 is an oral combination anticancer drug consisting of the 5-fluorouracil prodrugtegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate. In this combination 5-chloro-2, 4-dihydroxypyridine acts as a dihydropyrimidine dehydrogenase inhibitor, whereas potassium oxonate suppresses the gastrointestinal toxicity of tegafur[29]. In several studies of gastric cancer patients, S-1 has exhibited similar eﬃcacy and reduced toxicity compared with infusional 5-FU[9,30,31]. Capecitabine is also an oral fluoropyrimidinecarbamatethat is metabolized primarily in the liver and enzymatically converted to 5-fluorouracil by thymidine phosphorylase in tumor tissues. The levels of the enzyme thymidine phosphorylase are considerably higher in gastric cancers compared with normal tissue, which allows 5-fluorouracil to be concentrated in tumor tissues[32]. The efficacy and safety of capecitabine for advanced gastric cancer has been demonstrated[33], and a randomized phase III trial indicated that capecitabine can replace 5-FU for the treatment of advanced esophagogastric cancer[34].

This meta-analysis focused on the comparison of survival outcomes and toxicity between S-1-based regimens and capecitabine for the treatment of patients with gastric cancer. Only four randomized trials with 382 patients met our eligible criteria. Among the four studies, 1-year survival and overall response rate were selected as the primary study endpoints. Although overall survival is considered to be the most clinically meaningful measure of the treatment effect in cancer patients, only two of the studies analyzed overall survival; these results did not exhibit sufficient robustness for the meta-analysis. The results indicate that treatment with regimens containing capecitabine were equally as effective as S-1-containing chemotherapies in patients with gastric cancer with regard to 1-year survival and overall response rate. This result was consistent with the results of the four included studies[20-23].

The most suitable treatment regimen for an individual patient is not only dependent on treatment efficacy but also involves other factors, such as toxicity[35]. S-1 and capecitabine were both well tolerated, and no treatment-related deaths were reported in the selected studies. The most frequent hematologicaltoxicities were neutropenia and thrombocytopenia, and no meaningful differences in hematologic toxicities were noted between the two treatment agents. The most frequently observed grade 3 or 4 non-hematologic toxicities included nausea and vomiting, and no meaningful differences were noted between the two treatment agents. The only notable non-hematologic difference in adverse events was the increased incidence of hand–foot syndrome in the capecitabine group compared with the S-1 group. Hand–foot syndrome is a characteristic non-hematologic toxicity of capecitabine, leading to treatment delays or dose reductions in many patients. Given these findings, we suggest that S-1 is superior to capecitabine for the treatment of gastric cancer.

Although this meta-analysis was based on RCTs and properly conducted, there were still some limitations to our study. One major limitation was the number of selected studies was quite small, and this limited number of studies likely did not reflect the actual situation. In addition, only two studies analyzed overall survival, and these results did not exhibit sufficient robustness for the meta-analysis. However, 1-year survival and overall response rate, which are the most meaningful clinical measures of treatment efficacy in cancer patients, were analyzed.

In summary, although S-1 demonstrated no survival advantage over capecitabine, it resulted in a considerably lower incidence of hand–foot syndrome than capecitabine, thereby suggesting that S-1 is superior to capecitabine for the treatment of gastric cancer.

**COMMENTS**

***Background***

Gastric cancer is the second leading cause of cancer-related deaths globally and most of patients with gastric cancer are diagnosed in an incurable stage. Systemic chemotherapy have been proved to decrease the risk to relapse and improve survival and quality of life for advanced gastric cancer patients, combination regimen containing 5-ﬂourouracil is most commonly used worldwide. S-1 and capecitabine are both oral fluoropyrimidinecarbamate. The efﬁcacy of the oral capecitabine in gastrointestinal cancers has been investigated in a series of studies. Adjuvant chemotherapy with S-1 had been recommended in Japan. We aim to systematically compare the effects between S-1 and capecitabine against gastric cancer for better understanding the efficacy, safety, and feasibility of these anticancer drugs.

***Research frontiers***

Systemic chemotherapy is a important treatment for advanced gastric cancer patients, S-1 and capecitabine were both proved to be effective in the treatment of gastric cancer, but the efficacy, safety, and feasibility of S-1 *vs* Capecitabineremains unknown.

***Innovations and breakthroughs***

The authors performed a meta-analysis to systematically compare the effects between S-1 and capecitabine against gastric cancer for better understanding the efficacy, safety, and feasibility of these anticancer drugs. It may contribute to the better treatment and quality of life for the patients with advanced gastric cancer.

***Applications***

The results showed that S-1 are not effective than capecitabine in gastric cancer patients, but less toxicity in hand foot syndrome.

***Peer review***

In this manuscript, Peng *et al* determined that S-1 are not effective than capecitabine in gastric cancer patients, but less toxicity in hand foot syndrome. The efﬁcacy of the oral capecitabine in gastrointestinal cancers has been investigated in a series of studies, and Adjuvant chemotherapy with S-1 had been recommended especially in Japan. Thus they compare the effects between S-1 and capecitabine against gastric cancer and determined the conclusion. This conclusion is meaningful in the sense characterized the treatment of gastric cancer.

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**P-Reviewer:** **Chen L S-Editor:**Qi Y **L-Editor: E-Editor:**

**Table 1 Characteristics of trials included in meta-analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Patients (S-1/capecitabine)** | **S-1 regimen** | **Capecitabine regimen** |
| Kim *et al*[23] | 65/64 | S-1 80 mg/m2 per day d1-14 + Oxaliplatin 130 mg/m2 d1 21-d cycle | capecitabine 2000 mg/m2 per day d1-14+ Oxaliplatin 130 mg/m2 d1 21-d cycle |
| Lee *et al*[22] | 42/44 | S-1:BSA < 1.25 m2, 80 mg/d;  BSA: 1.25-1.5m2,100mg/d;  BSA > 1.5 m2, 120 mg /d; d1-28 42-d cycle | Capecitabine  2500 mg/m2 per day  d1–14 21-d cycle |
| Zhang *et al*[21] | 41/40 | S-1 80 mg/m2 per day d1-14 + Oxaliplatin 130 mg/m2 d1 21-d cycle | capecitabine 2000 mg/m2 per day d1-14+ Oxaliplatin 130 mg/m2 d1 21-d cycle |
| Xiong *et al*[20] | 42/44 | S-1 80 mg/m2 per day d1-14 +Docetaxel 25 mg /m2 d1, 8, 15 28-d cycle | capecitabine 1250 mg/m2 per day d1-14+Docetaxel 25 mg/m2 d1, 8, 15 28-d cycle |

**Table 2 Trial and patient characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Disease stage** | **Follow-up months** | **Trail randomization** | **Lost to follow** | **Survival analysis** |
| Kim *et al*[23] | Advanced gastric cancer, chemotherapy-naive | 0.5-39.2 | Yes | Recorded | ITT |
| Lee *et al*[22] | Elderly patients (aged ≥ 65 y)Advanced gastric cancer | capecitabine:21.9;  S-1: 21.7 | Yes | Recorded | ITT |
| Zhang *et al*[21] | gastric cancer after surgery | 24 | Yes | Recorded | Evaluable |
| Xiong *et al*[20] | Advanced gastric cancer, chemotherapy-naive | 2- 28 | Yes | Recorded | ITT |

**Figure 1 Flow diagram for studies evaluating S-1 vscapecitabinefor gastric cancerthat were included in thismeta-analysis.**

371 reports included on titles and abstracts using key word searches

Studies excluded after review of abstracts (*n* = 350)

Main purpose is not for

assessment of effects about

probiotics

21 reports considered

75 reports excluded: other than review articles, letters, case reports, lack of control group, not RCT and others

Total studies included in

the meta-analysis (*n* = 4)

**Figure 2 One year survival rate of S-1 regiment vscapecitabine regiment.**



**Figure 3 Overall response rate of S-1 regiment vscapecitabine regiment.**



**Figure 4 Nausea of S-1 regiment vscapecitabine regiment.**



**Figure 5 Toxicity of S-1 regiment vscapecitabine regiment.**



**Figure 6 Publication bias was assessed by funnel plot.**

