The efficacy and safety of capecitabine-based versus S-1-based chemotherapy for metastatic or recurrent gastric cancer: a systematic review and meta-analysis of clinical randomized trials

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Background: Gastric cancer (GC), particularly unresectable, metastatic, or recurrent GC, has been characterized by unfavorable prognosis. This meta-analysis of clinical randomized phase II trials was conducted to systematically evaluate the efficacy and safety of capecitabine-based versus S-1-based chemotherapy for metastatic or recurrent GC.

Methods: We searched PubMed, Embase, Web of Science, and Cochrane Library databases to identify studies eligible for the present analysis. Data were collected from inception to June 20th, 2019. Outcomes included objective response rate (ORR); 6-, 12-, and 18-month progression-free survival (PFS); 1-, 2-, and 3-year overall survival (OS); and adverse events. A meta-analysis was conducted using a random-effects model, and a sensitivity analysis was conducted to examine whether the results of the meta-analysis were robust. Risk ratio (RR) or hazard ratio (HR) with 95% confidence interval (CI) was reported as the main evaluation parameters.

Results: Six eligible studies with 561 subjects were included in the present meta-analysis. There was no significant difference between S-1-based and capecitabine-based chemotherapy in ORR (RR = 1.17, 95% CI: 0.95–1.44, P = 0.13, I² = 0%); 6-month (HR = 0.94, 95% CI: 0.77–1.14, I² = 0%), 12-month (HR = 0.89, 95% CI: 0.61–1.31, I² = 0%), and 18-month PFS (HR = 1.02, 95% CI: 0.55–1.91, I² = 0%); 1-year (HR = 0.99, 95% CI: 0.83–1.18, I² = 0%), 2-year (HR = 0.90, 95% CI: 0.58–1.42, I² = 0%), and 3-year OS (HR = 1.08, 95% CI: 0.50–2.34, I² = 0%). However, the capecitabine-based chemotherapy had a higher incidence in all grades of hand-foot syndrome (HFS) (RR = 3.41, 95% CI: 1.98–5.90, P < 0.01, I² = 39%) and grades 3–4 neutropenia (RR = 1.62, 95% CI: 1.05–2.51, P = 0.03, I² = 0%).

Conclusions: In terms of efficacy, capecitabine-based chemotherapy and S-1-based chemotherapy had similar short-term outcomes. Regarding safety, we recommend S-1-based chemotherapy for patients with metastatic or recurrent GC prior to capecitabine-based treatment.

Keywords: Capecitabine; meta-analysis; randomized controlled trials (RCTs); stomach neoplasms; S-1

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Introduction

Gastric cancer (GC), particularly the unresectable, metastatic, or recurrent type, has been characterized by unfavorable prognosis. According to the 2018 Global Cancer Statistics (1), the incidence and mortality of GC ranked fifth and third in the general population, respectively. Although various therapeutic approaches, like palliative surgery, cytotoxic therapy, targeted therapy, and immunotherapy, have been applied in GC treatment, the 5-year survival rate is unsatisfactory. The National Comprehensive Cancer Network (NCCN) and the guidelines from Europe recommend fluoropyrimidine (fluorouracil or capecitabine) plus a platinum compound (cisplatin or oxaliplatin) as the first-line chemotherapy of metastatic or recurrent GC (2,3). In contrast, the Korean guideline recommends S-1, an oral fluoropyrimidine, as a safe alternative to 5-Fluorouracil (5-Fu) (4). Moreover, S-1 plus cisplatin (SP) has been suggested to be the best regimen for patients with unresectable or recurrent GC in Japan (5). However, S-1 has not been incorporated into the first choice of GC treatment in China (6). Thus, it seems that S-1 and capecitabine in the GC therapeutic field are inconsistently valued across different regions. Two meta-analyses showed that there was no significant difference in objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) between S-1 and capecitabine-based chemotherapy, but a lower incidence of HFS was observed in the S-1 groups (7,8). In the study of Ye et al. (9), the 1-year OS and 1-year PFS between S-1-based and capecitabine-based chemotherapy were similar, but the ORR and adverse events like all-grade neutropenia and HFS were significantly different.

The prevailing evidence on the efficacy and safety of S-1 and capecitabine in the treatment of GC is acquired from patients with different stages of the disease, and the efficacy and safety of these treatments in patients with metastasis or recurrent GC are unclear. High-quality meta-analyses have been recognized as one of the key tools for acquiring reliable evidence for improving disease treatment (10-12). To this end, we conducted this meta-analysis of the published clinical randomized controlled trials (RCTs) relevant to the treatment of GC.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (13,14).

Search strategy

Two authors (Z Feng and X Hou) independently used the following search terms to identify relevant studies: “[gastric cancer OR stomach cancer OR gastric carcinoma OR stomach carcinoma OR gastric neoplasm OR stomach neoplasma] AND [S-1 OR tegafur OR FT207 OR utefos OR futraful OR sunfural OR uftoral OR florafur OR ftorafur OR BMS247616] AND [capecitabine OR xeloda]” from the PubMed, Embase, Web of Science, and Cochrane Library databases from inception to June 20th, 2019. The search was not restricted in any other way. The references of any literature found were screened to identify additional studies. Other studies were retrieved by manual searching of relevant journals.

Inclusion and exclusion criteria

We included RCTs that met the following inclusion criteria: (I) patients: adults who were diagnosed with metastatic or recurrent GC; (II) intervention: 1 treatment group receiving capecitabine-based therapy and the other receiving S-1-based therapy; (III) comparison: a capecitabine-based treatment group; (IV) outcomes: efficacy and safety data including ORR, OS, PFS, and adverse events were recorded; (V) language: published in English.

We excluded the following literature: (I) case reports, editorials, reviews and letters, animal studies, and conference papers; (II) studies with incomplete data; (III) repeated publications from the identical population or data used consistently (in such cases, only the report on the largest sample was included in this study).

Data extraction

The following information was extracted: (I) the first author and the year of publication; (II) the sample size, age, gender, and therapeutic regimen; (III) ORR, OS, and PFS; (IV) adverse events. Two reviewers (Z Feng and P Yan) independently conducted literature screening, data extraction, and quality assessment of the trials. When reviewers had a disagreement, a third reviewer (J Feng) intervened until a consensus was achieved.
Primary and secondary endpoints

The primary endpoint of the meta-analysis was efficacy, including ORR, PFS, and OS. The rate of adverse events, such as anemia, neutropenia, thrombocytopenia, anorexia, asthenia, diarrhea, HFS, and stomatitis, were regarded as secondary endpoints.

Assessment of publication biases

The risk of bias in the included RCTs was assessed according to the Cochrane Handbook version 5.1.0. The biases included detection bias, selection bias, reporting bias, performance bias, attrition bias, and other potential biases. The methodological quality was classified as having a low, high, or unclear risk of bias. The risk of bias assessment was completed independently by two reviewers, and any conflicts were resolved by a third reviewer (15-17).

Statistical analysis

The pooled estimates for dichotomous variables were reported as hazard ratio (HR), or risk ratio (RR) with 95% confidence intervals (CIs) and the results were presented as Forest plots. If no events were reported for one group in comparison, a value of 0.5 was added to both groups for each study (18). Based on the recommendation of the Cochrane Handbook (16), trials with no events in both groups were not included in the meta-analysis when RRs were calculated.

If a study did not report the OS or PFS data, all data were extracted from Kaplan-Meier survival curves by utilizing the software Engauge Digitizer (version 4.1, http://sourceforge.net/projects/digitizer). A random-effects model was applied to all pooled results. Heterogeneity was estimated based on the $I^2$ statistic. $I^2 < 50\%$ indicated low heterogeneity, whereas $I^2 \geq 50\%$ denoted high heterogeneity. This meta-analysis was implemented using the R software (version 3.5.1, https://cran.r-project.org/) and RevMan 5 software (version 5.0.25, http://ims.cochrane.org/revman/download). All P values were two-tailed, and P values $< 0.05$ were considered statistically significant.

Subgroup meta-analyses were conducted to investigate any potential sources of heterogeneity among studies. To explore the stability of this meta-analysis, we performed a sensitivity analysis by sequentially omitting individual studies. Finally, the funnel plots and the Egger’s and Begg’s tests were used for examining the potential for publication bias.

Results

Study selection

Study selection is shown in the flow chart in Figure 1. A total of 1,001 relevant studies were identified. After checking duplicated records and reviewing their titles and abstracts, 990 studies were excluded. The remaining 11 studies were assessed by full-text review. Ultimately, 6 studies were included.

Basic characteristics of the eligible studies

The characteristics of the eligible studies are summarized in Table 1. Two studies compared capecitabine monotherapy to S-1 monotherapy (19,20), another two studies compared capecitabine plus cisplatin (XP) to S-1 plus cisplatin (SP) (21,22), one study compared capecitabine plus oxaliplatin (CAPOX) to S-1 plus oxaliplatin (SOX) (23), and one study compared nivolumab plus capecitabine plus oxaliplatin (Niv + CAPOX) to nivolumab plus S-1 plus oxaliplatin (Niv + SOX) (24). All eligible studies were conducted in Japan or Korea.

Risk of bias in individual studies

Among the six RCTs, the risk of bias was high due to the lack of blinding of participants, study personnel, and outcome assessment. Information on random sequence generation and allocation concealment were unclear in three of these studies. A summary of the proportion of trials with low, unclear, and high bias in each domain is shown in Figure 2.

A meta-analysis of ORR

ORR was identified in six studies. Based on the random-effects model analysis, we found no significant (Figure 3) difference between the two treatment groups (RR =1.17, 95\% CI: 0.95–1.44, P=0.13, $I^2$ =0\%).

A meta-analysis of PFS

The meta-analysis showed no significant differences (Figure 4) between the two groups in terms of 6-, 12-, and 18-month PFS (RR =0.94, 95\% CI: 0.77–1.14, $I^2$ =0\%);
RR =0.89, 95% CI: 0.61–1.31, I² =0%; RR =1.02, 95% CI: 0.55–1.91, I² =0%; respectively).

A meta-analysis of OS

There were no significant differences between the two treatment groups in a meta-analysis of 1-, 2-, and 3-year OS (HR =0.99, 95% CI: 0.83–1.18, I² =0%; HR =0.90, 95% CI: 0.58–1.42, I² =0%; HR =1.08, 95% CI: 0.50–2.34, I² =0%; respectively) (Figure 5).

A meta-analysis of adverse events

The meta-analysis of adverse events among the eligible trials is presented in Table 2. Anemia and anorexia were the most common toxicities in both groups. No significant difference was found in total adverse events between the groups (RR =1.07, 95% CI: 0.99–1.15, P=0.08, I² =58%), but the incidence of HFS in the capecitabine-based group was higher than that of the S-1-based group (RR =3.41, 95% CI: 1.98–5.90, P<0.01, I² =39%).

Subgroup analysis

Subgroup analyses (Table 2) for grade 1–2 and grade 3–4 adverse events indicated that the incidence of HFS was also increased in the capecitabine-based group (RR =3.00, 95% CI: 1.45–6.19, I² =59%, P<0.01; RR =4.74, 95% CI: 1.31–17.11, I² =0%, P=0.02; respectively). In addition, analysis of grade 3–4 adverse events showed a higher incidence of neutropenia (RR =1.62, 95% CI: 1.05–2.51, I² =0%, P=0.03) in the capecitabine-based group. No statistically significant differences were found in other adverse events between the two treatment groups.

Publication bias and sensitivity analysis

The results of the sensitivity analysis showed that the present meta-analysis is stable, as revealed by the asymmetrical shape of the funnel plot (Figure 6). Furthermore, formal tests showed no substantial publication bias (P=0.695 for the Egger’s test; P=0.347 for the Begg’s test). The final results were not significantly influenced by a single study (Table 3). This suggests that the conclusions of the meta-analysis are robust.

Discussion

The principal findings of this study were the following: (I) between the capecitabine-based and S-1-based chemotherapy for the patients with metastasis or recurrent GC, and there were no significant differences in ORR; 6-,
Capecitabine and S-1 are both oral substitutes for 5-Fu. Capecitabine has a proven selection towards tumor cells and thus has potentially significant anti-tumor activity along with lower toxicity. It is therefore considered to be highly effective for patients with recurrent or metastatic GC in Western countries (25). Several studies showed that capecitabine-based chemotherapy is as effective as 5-Fu-based for improving prognosis and reducing 

12-, and 18-month PFS; and 1-, 2-, and 3-year OS. (II) Compared to S-1-based chemotherapy, patients treated with capecitabine-based had significantly higher incidences of all-grades HFS and grades 3–4 neutropenia, but there was no significant difference in total adverse events between the two treatment groups.

Capecitabine and S-1 are both oral substitutes for 5-Fu.

### Table 1: Study and patient baseline characteristics

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<tbody>
<tr>
<td>Lee</td>
<td>NCT00278863 (phase II) Korea [2004–2006] 46/45</td>
<td>Cap</td>
<td>1,250 mg/m², bid, days 1–14, q3w</td>
<td>71 [66–78]</td>
<td>30 (65.2)</td>
<td>2 [1–14]</td>
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<td></td>
<td></td>
<td>S-1</td>
<td>40–60 mg/m², bid, days 1–28, q6w</td>
<td>71 [65–82]</td>
<td>37 (82.2)</td>
<td>5 [1–22]</td>
<td></td>
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<tr>
<td>Kim</td>
<td>NCT00580359 (phase II) Korea [2007–2010] 54/53</td>
<td>Cap</td>
<td>1,250 mg/m², bid, days 1–14, q3w</td>
<td>71 [65–78]</td>
<td>44 (81.5)</td>
<td>5 [1–32]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>S-1</td>
<td>40 mg/m², bid, days 1–14, q3w</td>
<td>72 [65–81]</td>
<td>39 (73.6)</td>
<td>4 [1–26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawakami</td>
<td>UMIN000006755 (phase II) Japan [2011–2017] 43/41</td>
<td>XP</td>
<td>1,000 mg/m², bid, days 1–14, q3w; Cis: 80 mg/m², on day 1, q3w</td>
<td>64 [34–79]</td>
<td>36 (83.7)</td>
<td>NA</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>SP</td>
<td>40–60 mg/m², bid, days 1–21, q5w; Cis: 60 mg/m², on day 8, q5w</td>
<td>68 [38–77]</td>
<td>33 (80.5)</td>
<td>NA</td>
<td></td>
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<tr>
<td>Nishikawa</td>
<td>NCT01406249 (phase II) Japan [2011–2013] 55/55</td>
<td>XP</td>
<td>1,000 mg/m², bid, days 1–14, q3w; Cis: 80 mg/m², on day 1, q3w</td>
<td>65 [31–74]</td>
<td>45 (81.8)</td>
<td>4 [1–17]</td>
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<td></td>
<td></td>
<td>SP</td>
<td>40 mg/m², bid, days 1–21, q5w; Cis: 60 mg/m², on day 1, q5w</td>
<td>65 [44–74]</td>
<td>30 (54.5)</td>
<td>5 [1–17]</td>
<td></td>
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<tr>
<td>Kim</td>
<td>NCT00580359 (phase II) Korea [2008–2009] 64/65</td>
<td>CAPOX</td>
<td>1,000 mg/m², bid, days 1–14, q3w; Oxa: 130 mg/m², on day 1, q3w</td>
<td>61 [20–75]</td>
<td>45 (70.3)</td>
<td>8 [1–28]</td>
<td></td>
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<td></td>
<td></td>
<td>SOX</td>
<td>80 mg/m², bid, days 1–14, q3w; Oxa: 130 mg/m², on day 1, q3w</td>
<td>60 [28–77]</td>
<td>44 (67.7)</td>
<td>6 [1–34]</td>
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<td>Boku</td>
<td>NCT02746796 (phase II) Japan and Korea [2016–2017] 19/21</td>
<td>Niv + CAPOX</td>
<td>Niv: 360 mg, on day 1, q3w; Cap: 1,000 mg/m², bid, days 1–14, q3w; Oxa: 130 mg/m², on day 1, q3w</td>
<td>65 [39–80]</td>
<td>15 (78.9)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Niv + SOX</td>
<td>Niv: 360 mg, on day 1, q3w; S-1: 40 mg/m², bid, days 1–14, q3w; Oxa: 130 mg/m², on day 1, q3w</td>
<td>61 [37–77]</td>
<td>12 (57.1)</td>
<td>NA</td>
<td></td>
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</tbody>
</table>

Cap, capecitabine; Cis, cisplatin; Oxa, oxaliplatin; Niv, nivolumab; XP, capecitabine plus cisplatin; SP, S-1 plus cisplatin; CAPOX, capecitabine plus oxaliplatin; SOX, S-1 plus oxaliplatin; bid, bisindie; q3w, every 3 weeks; q5w, every 5 weeks; q6w, every 6 weeks; NA, not available.
recurrence, while it exhibits a higher incidence of HFS (26,27). S-1 is composed of tegafur, gimeracil and oteracil. Gimeracil saves the active form of S-1 by inhibiting dihydropyrimidine dehydrogenase, and oteracil decreases the phosphorylation of 5-Fu through combining orotate phosphoribosyltransferase in the gastrointestinal tract, all of which renders S-1 highly effective with low toxicity (28). Clinical trials on S-1 regimens in Japan had revealed that S-1 has a demonstrable effect on GC (29).

Compared to 5-Fu, S-1-based chemotherapy was superior in terms of drug-disease response rate, PFS, and OS for patients with GC (30-32). Meanwhile, S-1-based chemotherapy in GC was satisfactory in East Asia (20,33-38), but numerous investigators in Western countries questioned the benefits of this treatment as S-1 was found to have higher toxicity even at low doses for patients with advanced metastatic disease in Western trials (39). This discrepancy might be explained by the difference of gene polymorphisms encoding drug-metabolizing enzymes between Asian and Western populations (40).

RCTs and meta-analyses have been performed for identifying the better outcomes in treating GC between capecitabine-based and S-1-based regimens (7,8,19-24, 41-43). However, there is no consistent conclusion from these studies. One meta-analysis pointed out that, compared to capecitabine-based therapy, S-1-based chemotherapy was associated with similar anti-tumor efficacy and a better safety profile (42). However, another meta-analysis indicated that S-1 was not as effective as capecitabine in the treatment of GC (43). A systematic review and meta-analysis of six RCTs (one of RCTs was published in Chinese) and two retrospective studies of capecitabine-based and S-1-based regimens treatments for GC reported that S-1-based therapy might be a better choice for advanced GC patients due to the higher incidences of HFS and neutropenia in capecitabine-based therapy (9).

The longest time of efficacy evaluation, for the comparison between capecitabine-based and S-1-based therapy, was within 1 year of the currently published meta-analysis. Thus, we conducted the present meta-analysis to investigate a longer period of PFS and OS and to gain more evidence on drug-related efficacy. The result of our meta-analysis suggested that there was no difference in ORR between capecitabine-based and S-1-based therapy, which revealed that both regimens could be used as first-line therapy for the patients with metastatic or recurrent GC among Asian populations. PFS did reflect the progression of the lesion earlier. However, unlike PFS, OS was not as effective in observing changes in disease over time (44). Undoubtedly, longer periods of PFS and OS were better manifestations of optimal clinical benefits for GC patients.

We thus analyzed the 6-, 12-, 18-month PFS and the 1-, 2-, 3-year OS, respectively. As to the longest-follow-up PFS or the shortest-follow-up PFS, no significant differences were found between the two treatment groups. Similar results were found for the longest-follow-up OS and the shortest-follow-up OS. Taken together, these results indicate that capecitabine-based and S-1-based regimens have similarly efficacy for the treatment of GC.

In the overall analysis of adverse events, our results showed that there was no significant difference between capecitabine-based and S-1-based therapy. In the subgroup analysis, we analyzed eight types of the most common adverse events according to the grade-level from six studies and found that the incidence of all grades HFS and grades 3–4 neutropenia in GC patients treated with capecitabine-based therapy was higher than that among patients treated.
with S-1-based therapy. HFS is the most common non-hematological toxicity caused by capecitabine, and adversely affects the quality of life while decreasing the efficacy of treatments. Although urea cream and celecoxib are effective in treating HFS, further studies are needed to develop more specific medicines (45,46). Therefore, according to our results, S-1-based chemotherapy displayed high efficacy for high-risk patients with HFS and intolerable hematological toxicity.

Heterogeneity is an important factor that affects the results of a meta-analysis. Since heterogeneity could not be completely ruled out in this study, a sensitivity analysis...
was performed to assess the robusticity of our findings. We found that no study affected the overall significance of the pooled estimates, and thus our findings are robust. Publication bias can introduce false-positive results in a meta-analysis. To evade possible biases, all the studies included were thoroughly assessed. Egger’s and Begg’s tests were performed to detect publication bias and no significant bias was found. These analyses of publication bias and

<table>
<thead>
<tr>
<th>Type</th>
<th>Cap group (n/N)</th>
<th>S-1 group (n/N)</th>
<th>I², %</th>
<th>P value (I²)</th>
<th>RR</th>
<th>95% CI</th>
<th>P value (TE)</th>
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<tbody>
<tr>
<td>Overall adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anemia</td>
<td>232/277</td>
<td>229/274</td>
<td>0</td>
<td>0.79</td>
<td>1.01</td>
<td>(0.96, 1.06)</td>
<td>0.77</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>145/277</td>
<td>123/274</td>
<td>0</td>
<td>0.86</td>
<td>1.17</td>
<td>(0.99, 1.38)</td>
<td>0.06</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>128/277</td>
<td>128/274</td>
<td>37</td>
<td>0.16</td>
<td>1.00</td>
<td>(0.79, 1.26)</td>
<td>0.97</td>
</tr>
<tr>
<td>Anemia</td>
<td>197/277</td>
<td>191/274</td>
<td>0</td>
<td>0.42</td>
<td>0.98</td>
<td>(0.90, 1.07)</td>
<td>0.69</td>
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<td>Asthenia</td>
<td>166/277</td>
<td>162/274</td>
<td>5</td>
<td>0.38</td>
<td>0.95</td>
<td>(0.86, 1.04)</td>
<td>0.26</td>
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<td>Diarrhea</td>
<td>90/277</td>
<td>104/274</td>
<td>6</td>
<td>0.38</td>
<td>0.87</td>
<td>(0.69, 1.09)</td>
<td>0.24</td>
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<tr>
<td>HFS</td>
<td>104/277</td>
<td>29/274</td>
<td>39</td>
<td>0.14</td>
<td>3.41</td>
<td>(1.98, 5.90)</td>
<td>0.01</td>
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<tr>
<td>Stomatitis</td>
<td>70/277</td>
<td>51/274</td>
<td>40</td>
<td>0.14</td>
<td>1.39</td>
<td>(0.87, 2.23)</td>
<td>0.17</td>
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<tr>
<td>Total</td>
<td>58</td>
<td></td>
<td>0.01</td>
<td>1.07</td>
<td>(0.99, 1.15)</td>
<td>0.08</td>
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</table>

| Grades 1–2            |                |                |       |              |         |                  |              |
| Anemia                | 200/277        | 193/274        | 10    | 0.35         | 1.05    | (0.96, 1.16)     | 0.27         |
| Neutropenia           | 100/277        | 96/274         | 0     | 0.86         | 1.04    | (0.84, 1.30)     | 0.72         |
| Thrombocytopenia      | 108/277        | 108/274        | 40    | 0.14         | 1.00    | (0.75, 1.33)     | 0.99         |
| Anorexia              | 169/277        | 159/274        | 0     | 0.75         | 1.07    | (0.94, 1.22)     | 0.28         |
| Asthenia              | 145/277        | 148/274        | 0     | 0.90         | 0.93    | (0.81, 1.06)     | 0.29         |
| Diarrhea              | 82/277         | 90/274         | 0     | 0.83         | 0.91    | (0.71, 1.15)     | 0.43         |
| HFS                   | 87/277         | 29/274         | 59    | 0.03         | 3.00    | (1.45, 6.19)     | 0.01         |
| Stomatitis            | 66/277         | 49/274         | 39    | 0.15         | 1.36    | (0.83, 2.14)     | 0.24         |
| Total                 | 32             |                | 0.02  | 1.06         | (0.98, 1.15) | 0.15     |

| Grades 3–4            |                |                |       |              |         |                  |              |
| Anemia                | 32/277         | 36/274         | 0     | 0.48         | 0.93    | (0.59, 1.45)     | 0.74         |
| Neutropenia           | 45/277         | 27/274         | 0     | 0.97         | 1.62    | (1.05, 2.51)     | 0.03         |
| Thrombocytopenia      | 20/277         | 20/274         | 0     | 0.81         | 0.99    | (0.56, 1.75)     | 0.97         |
| Anorexia              | 28/277         | 32/274         | 4     | 0.39         | 0.83    | (0.51, 1.36)     | 0.45         |
| Asthenia              | 21/277         | 14/274         | 0     | 0.81         | 1.35    | (0.71, 2.57)     | 0.36         |
| Diarrhea              | 8/277          | 14/274         | 0     | 0.59         | 0.78    | (0.33, 1.88)     | 0.58         |
| HFS                   | 17/277         | 0/274          | 0     | 0.81         | 4.74    | (1.31, 17.11)    | 0.02         |
| Stomatitis            | 4/277          | 2/274          | 0     | 0.60         | 1.83    | (0.49, 6.86)     | 0.37         |
| Total                 | 0              |                | 0.89  | 1.14         | (0.93, 1.41) | 0.21     |

N, the total number of the sample; n, the total number of events; TE, total event; RR, risk ratio; HFS, hand foot syndrome.
sensitivity indicated that the conclusions of our study are solid.

There are several limitations to our research. Firstly, only 6 phase II trials with 561 individuals were included; therefore, additional high-quality RCTs are needed to validate the findings of this study better. Secondly, all studies are open-label, which might thus influence the outcomes. Thirdly, patients included in all studies were all from Asia, and hence the conclusions may not be generalizable to Western populations. Lastly, HRs and 95% CI, which were extracted from the Kaplan-Meier survival curves, might have influenced the pooled results.

Conclusions

In terms of efficacy, capecitabine-based chemotherapy and S-1-based chemotherapy have similar short- and medium-term outcomes. In terms of safety, we recommend S-1-based therapy as a top-priority regimen for patients with metastatic or recurrent GC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm.2020.04.26). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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