

April 26, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9766-review.doc).

Title: S-1 versus non-S-1 based chemotherapy in advanced gastric cancer: a meta-analysis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9766

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

To Reviewer 1:

1. There is no page number at the bottoms each page. Authors should describe them in the manuscripts.

Thank you for your careful review. And we have added the page number at the bottoms each page.

2. Is there any additional effect of 2nd or 3rd line chemotherapy after S-1 based first line chemotherapy? Author should add additional data and consideration, if possible.

Thank you very much for your constructive suggestion. The impact of first-line therapy on OS may be confounded by the second-line or third-line therapies. For example, in Hei-Cheul Jeung's study, more docetaxel/S-1 (DS) than docetaxel /Cisplatin (DC) patients were transferred to salvage chemotherapy (69% vs 41%), and many of them received cisplatin (23%), a generally favorable salvage treatment in AGC. And 23% of the DS patients who received second-line treatment showed an objective response, compared with only 9% of DC patients. And from the research of Narikazu Boku, second-line chemotherapy was given to 83% patients assigned continuous infusion of fluorouracil and 74% assigned S-1. But the additional effects of follow-up treatments were not reported minutely in most of the eligible trials, so we can not analysis the possible impact on survival. How to choose 2nd or 3rd line chemotherapy after S-1 based first line chemotherapy is important and valuable on clinic. More studies should be done in this aspect. And we will continue to focus on related research. However, in our meta-analysis, the follow-up treatments obviously do not alter TTF and PFS, which also confirmed the advantage S-1 based chemotherapy.

3. Is there any reports concerning to the incidence of race-specific adverse

effect by S1 and capecitabine reported bibliographic?

Thank you for asking this question. We have searched and read the related papers. Some studies concerned to the incidence of race-specific adverse effect by S1 or capecitabine. According to the results came from different races, the incidence of grade 3/4 diarrhea of S-1 in the Japanese and Americans was 9% and 22%, respectively, and other toxicities were mild in both populations [1]. Tolerance of capecitabine is thought to be different in various ethnic [2]. The rates of grade 3/4 hand-foot syndrome (0–13% in Asian vs 11–17% in West) and grade 3/4 diarrhoea (2–5 vs 11–13%) tend to be lower, and the rate of grade 3/4 neutropenia (0–8 vs 1–2%) similar or higher [3–5]. And it is speculated that folic acid levels in diet may be responsible for these differences.

References:

- [1] Shirao K et al. Comparison of the efficacy, toxicity, and pharmacokinetics of a uracil/tegafur (UFT) plus oral leucovorin (LV) regimen between Japanese and American patients with advanced colorectal cancer: joint United States and Japan study of UFT/LV. *J Clin Oncol*. 2004; 22(17):3466–3474.
- [2] Haller DG et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol*. 2008; 26:2118–2123.
- [3] Cassidy J et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol*. 2002; 13:566–575.
- [4] Twelves C et al. Capecitabine as adjuvant treatment for III stage colon cancer. *N Engl J Med*. 2005; 352:2696–2704.
- [5] J-L Lee et al. A randomized multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer*. 2008; 99(4):584–590.

To Reviewer 2:

1. Funnel plot in Figure 2 is for judgment of publication bias. However, in result section, Figure 2 is described as for heterogeneity. Explanation of Figure 2 needs to be revised.

Thank you for pointing this out. We have added the following explanations of Figure 2 (now Figure 4) in the article. Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. Evidence of publication bias was detected by plotting funnel plots of HR. Studies were plotted in order of decreasing variance of the log HR. And no publication bias was detected for all comparisons. Here we showed the Begg's funnel plots for the comparison of OS (Egger's test: $P = 0.921$, Begg's test: $P = 0.851$; Figure 4).

2. Correction of some wrong spelling is needed.

Yes, we have checked the paper carefully and corrected the wrong spelling.

3. It seems to be better to add citation of reference in table 1.

Yes, and we have added the citations after the corresponding authors in table 1.

To Reviewer 3:

1. The work is well written and interesting because it focuses attention on a controversial issue in the treatment of AGC, but the authors should stress more clearly that these results are true especially in the Asian population, and should explain why.

Thanks for the kind suggestion. Only one of the trials researched by Ajani JA et al was come from non-Asian countries. According to the suggestion of the reviewer, we pooled the data from Asia countries, and gain the longer OS (HR = 0.87, 95%CI: 0.75-0.99, $p = 0.048$), PFS (HR = 0.78, 95%CI: 0.68-0.89, $p = 0.000$) and TTF (HR = 0.76, 95%CI: 0.64-0.91, $p = 0.003$) in the S-1 based group. And only grade 3 or 4 leukopenia was softer in the non-S-1 based chemotherapy (RR: 2.198, 95%CI: 1.403-3.443, $p = 0.001$). Up to now, one and only non-Asian global phase III trial gain a negative result about survival time in the S-1 based therapy. So the advantage of S-1 in the treatment of AGC is true especially in the Asian population. The most correlative factor in our opinion is that, the metabolic rate of conversion of S-1 to fluorouracil seems to differ in various ethnic populations. S-1 converted to 5-FU in the liver mainly by cytochrome P450 2A6 (CYP2A6). There is race difference in the polymorphism of CYP2A6, which affects the clinical outcomes of patients who are undergoing S-1-containing chemotherapy for AGC. Different races mean different gene expressions to a certain degree. So we think that, the expression of specific genes may finally decide the effectiveness of S-1. For example, Ichikawa W et al. 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. And Ishido K et al. proved that intratumoral TS expression is 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.

2. The authors could add in the reference section the review of Orditura et al published a month ago in WJG.

Thank you for the valuable suggestion. We have read this review carefully, and the progress in treatment of gastric cancer is introduced in detail. It is helpful for the writing and amendment of this manuscript. And we have added it in the reference section.

3 References and typesetting were corrected

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

Thank you again for publishing our manuscript in the *World Journal of*

Gastroenterology.

Sincerely yours,

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