Author Response Letter to Reviewers' Comments

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Title: Adjuvant Chemotherapy with S-1 plus Oxaliplatin Improves Survival of Patients with Gastric Cancer after D2 Gastrectomy: A Multicenter Propensity Score-Matched Study

Name of Journal: *World Journal of Clinical Cases*

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Dear Editor,

We thank you for your careful consideration and reviewers' thoughtful evaluations of our manuscript entitled "Adjuvant Chemotherapy with S-1 plus Oxaliplatin Improves Survival of Patients with Gastric Cancer after D2 Gastrectomy: A Multicenter Propensity Score-Matched Study".

We appreciate your response and overall positive initial feedback. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our study. Changes are highlighted in yellow in our revised manuscript. And we provide our point-by point response to the reviewers' comments below.

We hope that the revised manuscript will now be suitable for publication in your journal. Please do not hesitate to contact us with any questions or concerns regarding to the manuscript.

Yours sincerely,

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Response to comments from reviewer,

Reviewer code: 00182114

1. Author concluded that compared with XELOX regimen, SOX showed no significant difference in DFS and OS. The most common >3 grade adverse events of SOX regimen were neutropenia(22.6%), leukopenia (8.9%) and thrombocytopenia (5.6%). SOX significantly improves the long-term survival and have low adverse effect compared to XELOX. SOX may be a novel adjuvant chemotherapy regimen in GC patients. I ask some questions to author.

Response: We would like to express our sincere thanks to you for carefully and patiently reviewing our manuscript. Thanks for your comments.

2. Please tell me the reason why SOX is much lower compared to XELOX from the point of the frequency of drug side effect.

Response: Thanks for your valuable time in reviewing our manuscript. We compared the frequency of drug side effects of our study with CLASSIC trial and found more neutropenia (75.0% vs. 60%) and thrombocytopenia (37.9% vs. 26%) of SOX, but fewer nausea (51.6% vs. 66%), vomiting (29.8% vs. 39%) and peripheral neuropathy (52.4% vs. 56%). However, Guoxiu Wang et al. who conducted a phase 2 study of adjuvant SOX in gastric cancer, reported higher frequency of nausea (77.8% vs. 66%), peripheral neuropathy (61.1% vs. 56%) and similar frequency of vomiting (38.9% vs. 39%). Those were different from our study. Because our study is a retrospective study, it is possible for our study that part of side effects were not registered in the medical record system.

3. S-1 plus cisplatin (SP) is one of the standard first-line chemotherapies for AGC in the East Asia. Please compared the safety and efficacy of S-1 plus oxaliplatin (SOX) with those of SP.

Response: Thanks for your constructive suggestion. As we know, SP is a effective and relatively safe regimen in advanced gastric cancer. However, because of the relatively more digestive tract adverse reaction, renal toxicity, leukopenia, and thromboembolic events of cisplatin, few of studies about SP regimen were conducted for adjuvant chemotherapy in gastric cancer. Daisuke T et al. reported a clinical trial about adjuvant chemotherapy with SP for stage III gastric cancer and 3-year recurrence-free survival rate (74.1%) and 3-year overall survival rate (84.5%) was reported, but the side effects of SP was not mentioned. So, it's difficult to make direct comparisons between SOX and SP for their safety and efficacy in adjuvant treatment of gastric cancer.

Reviewer code: 02546253

1. This is a study that examined the safety and efficacy of adjuvant chemotherapy for stage IB to III gastric cancer after gastrectomy with D2 lymph node dissection (four-center trials). In this study, it was revealed that both DFS and OS could be more improved significantly in adjuvant chemotherapy group than surgery alone group by comparing of "surgical alone group vs adjuvant SOX" and "adjuvant SOX vs XELOX" using propensity score-matching. Since the result of ACTS-GC became clear, adjuvant chemotherapy by oral S-1 was standardized for stage II and III gastric cancer. Accordingly, it became difficult to compare the survival outcome between surgery alone group and adjuvant chemotherapy group other than oral S-1. Under the circumstances, it may be worthwhile to be able to compare the surgery alone group with the adjuvant SOX group in this study at the same time as ACTS-GC.

Response: We would like to express our sincere thanks to you for carefully and patiently reviewing our manuscript. Thanks for your comments.

2. However, as described as "Limitation", patients in surgery alone group may have not had adjuvant chemotherapy for reasons such as some kind of comorbidities, poor PS

(performance status), bad economic situation and so forth. Namely, there is a possibility that the worse population was selected for surgery alone group. To make accurate comparisons regarding the treatment outcomes between the presence or absence of adjuvant chemotherapy, propensity score-matching including PS and ASA (American Society of Anesthesiologists) classification should be performed not only in the tumor factor. The treatment outcomes of the surgery alone group in this study (DFS: 44.6%、OS: 45.8%) are poor compared to ACTS-GC trial (DFS: 53.1%、OS: 61.1%) and CLASSIC trial (DFS: 53%、OS: 69%), and the reason may be also that the worse population was concentrated in surgery alone group.

Response: Thanks for your valuable time in reviewing our manuscript, and thanks for your constructive suggestion. For fear of the side effects of chemotherapy, such as alopecia, nausea, vomiting, quite a few patients in China reject adjuvant chemotherapy after surgery, espically before 2012. That is the reason why we have so many patients in surgery alone group. Secondly, all patients in our study underwent D2 dissection. Those patients usually have good performance status, otherwise surgery would not be allowed. Meanwhile, as the part of "Survival benefit of adjuvant SOX chemotherapy" showed, when comorbidity was added into propensity score-matching analysis, Similar outcomes were obtained. Thirdly, most patients in the surgery alone group of our study are stage III GC patients (70.94%), which is much higher than those of ACTS-GC trial (42.3%) and CLASSIC trial (49%). It may explain why the treatment outcomes of the surgery alone group in our study (DFS: 44.6%, OS: 45.8%) are poor compared to ACTS-GC trial (DFS: 53.1%, OS: 61.1%) and CLASSIC trial (DFS: 53%, OS: 69%).

3. Although this study pointed out the low completion rate of adjuvant chemotherapy in ACTS-GC trial and CLASSIC trial, there was no mention of what number of cycles was originally set for the SOX and the XELOX, and the treatment completion rate of them was also unknown.

Response: Thanks for your valuable time in reviewing our manuscript. We are very sorry that our study is a retrospective study, not a prospective study. For the reason that there were no standard chemotherapy cycle for SOX and XELOX before 2012, different oncologists made different decisions about the number of chemotherapy cycles. So, no originally number of chemotherapy cycles was set in the study. Our study included all GC patients with stage IB to III who received SOX or XELOX treatment, regardless of the number of cycles they conducted. Therefore, we didn't calculate the completion rate of SOX and XELOX in our study. But we showed the median cycles and total cycles of them. As the part of "Efficacy between SOX regimen and XELOX regimen" shows, "In adjuvant SOX group (57 patients), patients received 250 cycles chemotherapy in total with median cycles of 4. In adjuvant XELOX group (57 patients), patients received 258 cycles chemotherapy in total with median cycles of 5."

5. Most of previous reports regarding adjuvant SOX were Phase II trials, and few have shown long-term results. Most recently, Guoxiu Wang et al. reported DFS (75.9%) and OS (85.2%) for 3 years by adjuvant chemotherapy, SOX. According to this study, DFS and OS for 5 years by adjuvant SOX were shown, there is a possibility that it will support the selection of Adjuvant SOX.

Response: Thanks for your valuable time in reviewing our manuscript. We have added this study in the disccusion part of our manuscript.