Author's response to reviews

Title: Retrospective analyses of cisplatin-based doublet combination chemotherapy in patients with advanced gastric cancer

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Version: 2 Date: 22 July 2010

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Date: July 22, 2010

Dear Editor

BMC CANCER

Re: MS 1875994836243872 “Retrospective analyses of cisplatin-based doublet combination chemotherapy in patients with advanced gastric cancer”

We appreciate the opportunity to reply to the thoughtful review on our manuscript. We revised our manuscript according to the reviewer’s suggestions. Please find attached manuscript, which was revised and condensed to a shorter form. Our reply to your comments is listed on the next page, and the revisions are underlined in the text.

Sincerely yours,

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Editor’s comments and suggestions:

Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study.

-> Thanks for an important comment. An acknowledgement section in which the funding source was designated was added at the end of the manuscript.

Reviewer #1 (Dr Wan Yuanlian)’s comments and suggestions:

The study design was rational, and regimen selection and grouping were appropriate. Clinical data was reliable with proper statistical method used. The article title and abstract well described the content of their research. Their conclusions were objective and their reference citations were reasonable. Several details need to clarify before publication:

1. Drug dosage and administration methods should be described in more detail

# Four cisplatin-based regimens were used in this study. The paper showed the cisplatin dosage from 60 to 100mg/m2. The dosage of cisplatin in each study group and the reasoning for dose adjustment should be provided.

-> Thanks for the important comment. Considering this was a retrospective study in which the treating physician determined chemotherapy regimen for each patient, cisplatin dosage was varied for the preference of each physician. We referred in the Methods as “The treating physician determined chemotherapy regimen, as well as the initial dose of cisplatin, for each patient”.


In FP regimen, the method of 5-Fu administration was iv, either bolus intravenous injection or continuous intravenous infusion should be specified.

-> 5-day protracted infusion was used as the regimen regarded standard in Korea. We specified that in the Methods section.

2. The criteria on the efficacy evaluation needed

# RECIST criteria was used for assessment of therapeutic efficacy. The study only mentioned the use of abdominal pelvic CT and other methods. Please describe whether it was spiral CT and specify what other methods are.

-> Spiral CT is the prevalent technique involved in the most of Korean tertiary centers. We edited the sentence as “According to the guidelines and department policies, all tumor measurements were assessed after every 2 courses of chemotherapy, by using spiral abdominopelvic computed tomography (CT) scan and other tests that were used initially to stage the tumor”.

# Regarding to CR and PR patients, a confirmation evaluation after one month should be mentioned.

-> Thanks for the comment. A confirmation CT scans for response are standard method in Korea. A sentence regarding the confirmation CT was added “As a general principle for determining clinical response, a confirmatory CT scan was recommended at least 4 weeks apart”.

# Please indicate whether the therapeutic efficacy were evaluated by imaging experts?

-> As already stated in the Methods, only the survival data was updated at the time of analyses. Please note that the current manuscript contains retrospective data.

# In each study group, the total response rate was available. Additional
information about CR and PR rate should be provided.

-> Thanks for the suggestion. We observed only two patients with CR. “Objective responses to cisplatin-based chemotherapy were noted in 107 patients (response rate, 38%; 95% confidence interval [CI], 32-43%), including two complete responses seen in XP patients”.

3. The results show that performance status (ECOG 0-1 VS # 2) and peritoneal metastasis were prognostic factors associated with objective response rate, PFS and OS. The following questions need to address:

# According to Table 1 shows: ECOG # 2 patients in SP, DP and FP were 2-3 times more than XP group (only 5% in XP group). Considering baseline characteristic imbalanced in each group, how to interpret the results. XP group with more ECOG 0-1 patients could be the cause of high response rate.

-> This is an important comment. We think the imbalances you mentioned is likely related to the different outcomes. We added a sentence concerning the imbalance in the Results section “We noted that more DP patients had received adjuvant therapy involving 5-FU, less XP patients had an ECOG performance status of 2, and most of FP patients had peritoneal dissemination at the time of presentation”, as well as in the Discussion as “Our observation that PFS was shorter with DP or FP than XP or SP is likely related to negative prognostic factors influencing the choice of intravenous chemotherapeutic agents instead of oral ones. AGC patients who already had peritoneal dissemination, with or without ascites, could not tolerate oral agents.”.

# According to Table 1: 75% patients in FP group were found peritoneal metastasis, which was 1.38-1.6 times higher than XP, SP or DP groups. Imbalance in baseline characteristic in each group, how to interpret the results?

-> Thanks again for an important comment. Please refer to the
answer above.

# Since the baseline characteristic of FP and XP groups were comparable, the differences of PFS, OS (including the survival curve) and toxicity in these two group were warranted further statistical analysis.

-> We added a sentence comparing FP and XP in the Results “In particular, XP patients had a longer PFS that FP patients (hazard ratio, 0.79; 95% CI, 0.52-1.21; p=0.29)”.

4. Adverse events
# Pease indicate the criteria for toxicity evaluation.

-> A sentence was inserted in the Methods as “Toxicities were graded according the National Cancer Institute (NCI) criteria (CTCAE v3)”.

# Table 2 only showed that the overall incidence of grade 3-4 toxicity was not significantly different among four groups. The hematological toxicity and non-hematological toxicity should be separated for analysis. In addition, grade 3-4 toxicity in FP group appeared lower than other groups. Any interpretation from this observation?

-> Within the limitation of retrospective analysis, we thought the actual comparisons of each specific toxicity between treatment groups are not relevant. In addition, grade 3-4 toxicity in FP group (81%) was not different from other groups (88% for XP, 75% for SP, and 93% for DP). Thanks for the comment.

5. Please indicate the title of Figure 1 and the definition of the vertical axis.

-> We included the title of Figure 1 “Overall survival according to chemotherapy regimens”. 
Reviewer #2 (Dr Pompilui Piso)’s comments and suggestions:

This is an interesting paper on the effect of cisplatin based chemotherapy on advanced gastric cancer. In my opinion, some useful information can be taken from this manuscript to select appropriate patients for gastrectomy. The question is, however, what is really new in this paper? Platin derivates are in many countries standard for metastatic gastric cancer and, since MAGIC trial, they are used also in neoadjuvant treatment. The authors should focus on following aspects in the revised manuscript:

1. The inclusion of recurrent cancer in the group is problematic. The results should be treated separately and compared for primary advanced gastric cancer vs. recurrent cancer.

   -> Thanks for the suggestion. In situation of locally recurrent gastric cancer, chemotherapy is rarely involved in treatment strategies in Korea. What I mean is that all of the “recurrent” gastric cancer patients included in the current analysis had metastatic disease. To avoid possible confusion, we decided to edit the phrase as “(3) presence of metastatic disease”.

2. Why should be the prognosis better after gastrectomy? Is this true only for primary tumors? Should this suggest to perform always gastrectomy (to resect the primary tumor, even if asymptomatic)?

   -> This is an important comment. As you suggested, the role of cytoreductive surgery in metastatic disease is still disputed. However, in some studies including our previous one (Ref # 15, Ann Oncol 2007), it was suggested that patients with previous gastrectomy pursued favorable clinical course when compared with those without. The role of palliative surgery warrants further investigation, and a randomized trial (REGATTA study) is underway. We decided to add
sentences on this question in the Discussion “Although it is conceived that the rationale for offering palliative gastrectomy to patients with unresectable or metastatic gastric cancer is to avoid tumor bleeding, perforation, obstruction, or to improve the outcome by reducing tumor burden, the role of palliative gastrectomy in AGC patients with metastatic disease needs clarification [15]. A randomized trial (reductive gastrectomy for advanced tumor in two Asian countries, REGATTA, KGCA01/JCOG0705) is underway”.

3. Did any patients had a curative gastrectomy following partial response?
   -> None receive gastrectomy following clinical responses, considering the palliative nature of treatment.

4. Within patients with palliative gastrectomy, what was the reason to resect: bleeding, stenosis, other reason?
   -> Good comment. The rationale for offering surgery to metastatic GC patients is to avoid bleeding, perforation, or obstruction. Unfortunately, due in part to the retrospective nature of the study, identification of the exact causes of palliative gastrectomy for each patient was not possible.

5. Within those having recurrent tumor, how many had received also neoadjuvant chemotherapy and did they had a responded?
   -> Please note that neoadjuvant chemotherapy is not generally perceived standard in Korea. None were treated with neoadjuvant therapy.

6. How do the authors explain the higher response rate and improved PFS but no improvement of the OS? Is this difference relevant and why?
   -> One possible explanation is that >50% of patients received
second-line therapy. Although it is presently unclear whether second-line chemotherapy results in better outcome, salvage therapy could had an effect on the OS. We added a sentence in the Discussion as "While there was no relevant difference is OS between treatment groups, it is worth considering the possible role that second-line therapy could have had on survival. More than half of patients received second-line chemotherapy”.

7. Has been the quality of life analysis ?

-> Unfortunately the QOL was not assessed in the study. Please remember the current results were from a retrospective study.

8. Page 12, second row from bottom: it is the absence (not presence) of peritoneal dissemination

-> We are indebted for the comment. The sentence was edited.

9. What about oxaliplatinum. It should be mentioned in the manuscript because it has lower toxicity with fewer cumulative adverse events than cisplatinum and a better PFS.

-> We totally agree with your suggestion. A paragraph explaining about oxaliplatin was added at the end of the Discussion as “Although cisplatin is often used in combination with other agents, it is well known that cisplatin is associated with significant toxicity and usually requires a high level of clinical monitoring and supportive care including intensive intravenous hydration. Oxaliplatin-based regimens have been actively investigated to improve the efficacy and tolerability of combination chemotherapy for AGC patients [5, 23]. Oxaliplatin has significant activity against some cisplatin-resistant tumors and a favorable safety profile over cisplatin [24]”.