Format for ANSWERING REVIEWERS

November 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14085-review.doc).

Title: Weekly docetaxel and gemcitabine in previously treated metastatic esophageal squamous cell carcinoma

Author: Min-Young Lee, Ki Sun Jung, Hae Su Kim, Ji Yun Lee, Sung Hee Lim, Moonjin Kim, Hyun Ae Jung, Sung Min Kim, Jong Mu Sun, Myung-Ju Ahn, Jeeyun Lee, Se Hoon Park, Seong Yoon Yi, In Gyu Hwang, Sang-Cheol Lee, Hee Kyung Ahn, Do Hyoung Lim, Soon Il Lee, Keon Woo Park

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14085

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

(1) Please submit related registration information of ethics.

→ Thanks for your comments. I provided the clinical trial registration information below text.

:: Clinical trial registration: This study is registered at http://clinicaltrials.gov/show/NCT01469598. The registration identification number is NCT01469598.

(2) Reference 5 is misquoted on page 5 (1st paragraph). It should be replaced by a reference on esophageal squamous cell carcinoma.

→ I checked and revised reference as you had advised.

:: The combination of cisplatin and infusional 5-fluorouracil (5-FU) is the most commonly used regimen as palliative first-line chemotherapy for metastatic esophageal SCC[4-6].

:: Reference)

4 Scheithauer W. Esophageal cancer: chemotherapy as palliative therapy. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2004; 15 Suppl 4: iv97-100 [PMID: 15477344 DOI: 10.1093/annonc/mdh911]

5 Grunberger B, Raderer M, Schmidinger M, Hejna M. Palliative chemotherapy for recurrent and metastatic esophageal cancer. Anticancer research 2007; 27(4C): 2705-2714 [PMID: 17695436]

6 Ajani JA. Contributions of chemotherapy in the treatment of carcinoma of the esophagus: results and commentary. Seminars in oncology 1994; 21(4): 474-482 [PMID: 8042045]

(3) The dose of Docetaxel (35mg/m^2) needs to be justified.

→ I added below text and reference for our dose of docetaxel (35 mg/m^2)

:: Several phase I and II clinical trials have examined docetaxel administered in weekly doses of 30, 35, 40 mg/m^2. The weekly docetaxel 35mg/m^2 chemotherapy group produced less myelosuppression, and better compliance and response rates than the 3-weekly docetaxel or other weekly dose groups[21, 22]. Our clinical trial administered docetaxel at a weekly dose of 35 mg/m^2.

:: Reference)

21 Chen YM, Shih JF, Perng RP, Tsai CM, Whang-Peng J. A randomized trial of different docetaxel schedules in non-small cell lung cancer patients who failed previous platinum-based chemotherapy. Chest 2006; 129(4): 1031-1038 [PMID: 16608954 DOI: 10.1378/chest.129.4.1031]

22 Tanaka Y, Yoshida K, Sanada Y, Osada S, Yamaguchi K, Takahashi T. Biweekly docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy for advanced esophageal squamous cell carcinoma: a phase I dose-escalation study. Cancer chemotherapy and pharmacology 2010; 66(6): 1159-1165 [PMID: 20878160 PMCID: 2955920 DOI: 10.1007/s00280-010-1447-1]

(4) "The most common first-line chemotherapy regimen was 5-FU plus cisplatin (76%) followed by capecitabine plus cisplatin or paclitaxel (24%)" (1st paragraph, page 10). This is contradictory to the criteria of inclusion, which include "prior exposure to taxanes or gemcitabine" (1st paragraph, page 7).

→ I corrected that taxanes to docetaxel.

:: Patients with serious concomitant medical diseases prior to exposure to docetaxel or gemcitabine, who were pregnant or breast feeding, who had a history of significant neurologic or psychiatric disorders, or evidence of serious gastrointestinal bleeding were considered ineligible.

(5) In Discussion section, the authors need to quote historical data to show the advantage of docetaxel/gemcitabine as compared with other second-line regimen or palliative therapy without chemotherapy in terms of overall survival etc.

→ I added below text and references.

:: Recently, several studies on combination chemotherapy for second-line treatment of previously treated metastatic esophageal cancer have been conducted. Among them, there are two reports of combination chemotherapy including docetaxel as a second-line regimen in metastatic esophageal squamous cell carcinoma. Shim et al.[27] did a phase II study on docetaxel and cisplatin chemotherapy, which showed a response rate of 34.2%, a median PFS of 4.5 mo, and a median OS of 7.4 mo. However, this regimen showed toxicity with grade 3 or 4 neutropenia at 52.6%, asthenia at 31.6%, nausea at 18.4%, and neuropathy at 15.8%. In another phase II study using docetaxel and nedaplatin for patients previously treated with cisplatin and fluorouracil by Jin et al.[28], the reported response rates were 27.1%, the median PFS was 3.1 mo, and the median OS was 5.9 mo. This regimen showed toxicity of grade 3 or 4 of neutropenia at 19.6%, grade 1 to 4 anorexia at 47.8%, fatigue at 41.3%, and nausea/vomiting at 32.6%. The docetaxel-platinum based chemotherapy present similar response rates and survival data compared with the current study. However, the toxicity profile of platinum-based chemotherapy showed another important clinical problem. There are several cumulative platinum induced toxicities observed after platinum-based chemotherapy is used as a first-line treatment in esophageal SCC, including emesis, decrease in glomerular filtration rate (GFR), and neurotoxicity.

:: Reference)

27 Shim HJ, Cho SH, Hwang JE, Bae WK, Song SY, Cho SB, Lee WS, Joo YE, Na KJ, Chung IJ. Phase II study of docetaxel and cisplatin chemotherapy in 5-fluorouracil/cisplatin pretreated esophageal cancer. American journal of clinical oncology 2010; 33(6): 624-628 [PMID: 20142726 DOI: 10.1097/COC.0b013e3181bead92]

28 Jin J, Xu X, Wang F, Yan G, Liu J, Lu W, Li X, Tucker SJ, Zhong B, Cao Z, Wang D. Second-line

combination chemotherapy with docetaxel and nedaplatin for Cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2009; 4(8): 1017-1021 [PMID: 19542899 DOI: 10.1097/JTO.0b013e3181add9c7]

(6) Two previous studies may be quoted and compared with this study: Med Oncol 2007;24(4):407-12. OncoTargets Therapy 2014;7:1875-81.

→ As you had advised, I quoted these references.

(7) Typographical errors: Page 5 2nd Paragraph line 3- should be in the salvage setting in particular, the toxicity... Page 5 2nd Para line 10 - has not have Page 6 2nd Para line 2- As such, a weekly schedule... Page 10 Para 1 last line- should be but did not benefit (instead of was not benefited) Page 12 Para 3 line 1- should be "in the second-line"

→ Thanks for your comments. I corrected typographical errors that you pointed out.

(8) Suggest referencing Recist1.1 in methods section and not putting all the specific details. Ie clinical tumor response was assessed according to RECIST 1.1 [insert reference]

→ I inserted reference for RECIST criteria, and removed the specific details.

:: As the primary endpoint of this study was objective RR, the clinical tumor response was assessed according to the RECIST criteria version 1.1[18].

:: Reference)

18 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

(9) In discussion setting- cannot conclude low incidence of severe hematologic toxicities with 39% G3 neutropenia. You could conclude that it had an acceptable or tolerable toxicity profile.

→ I agree your opinion. So, I corrected below text.

:: The current study confirmed these results, the non-platinum combination of docetaxel 35 mg/m^2 and FDR gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 wk had an acceptable toxicity profile.

(10) Suggest some of the discussion section regarding historical data be moved to the introduction section and remove some of the repetition.

→ I corrected manuscript as you had advised. Some of the historical data moved to the introduction section and removed the repetition in discussion section.

:: Moved to the introduction section

When patients have failed platinum and fluoropyrimidine combination chemotherapy, it is commonly observed that patients experience a rapid clinical deterioration and decline in their performance status.

… For example, a clinical study by Hensely et al.[14] demonstrated an impressive 53% response rate in patients with predominantly uterine leiomyosarcoma. In this study, patients received gemcitabine 900 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8 with granulocyte-colony stimulation factor

(G-CSF) support every 3 wk.

:: Remove the repeat historical data in discussion section

In patients with metastatic esophageal SCC, the combination of 5-FU and platinum, either doublet or in combination with anthracyclines, constitutes the most frequently attempted chemotherapy regimen. However, there is no evidence that second- or further salvage chemotherapy may result in substantial prolongation of OS in patients with esophageal SCC, and there is potential for toxicity from the treatment. It is common observation that patients experience a rapid clinical deterioration and decline in their performance status after first-line chemotherapy failure.

(11) Some of the discussion should focus on the activity reported in the current setting in comparison to other second line regimens and focus on the advantages of the current schedule over alternative treatment options.

→ I added text and references in No. 5 comment/answer.

(12) There should be some discussion regarding the relative merits of fixed dose rate and standard gemcitabine dosing, particularly with regards to potential disadvantages of the fixed dose rate regimen (specifically myelosuppression).

→ I added below text and reference.

:: The issue of whether prolonged-infusion gemcitabine (10 mg/m^2/min) results in higher clinical response rates compared to bolus infusions has been addressed in a randomized trial in pancreatic cancer[10]. Grade 3 and 4 myelosuppression occurred with both the FDR infusion and the bolus infusion group. This result seemed to be more toxic with the FDR infusion. However, a higher incidence of dose modification or discontinuation of gemcitabine was not observed[10].

:: Reference)

10 Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2003; 21(18): 3402-3408 [PMID: 12885837 DOI: 10.1200/JCO.2003.09.140]

3 References and typesetting were corrected

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

Sincerely yours,

Min-Young Lee
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Fax: +82-2-3410-1754
E-mail: redmin07@gmail.com