Mar. 20th, 2019

Dear editor:

RE: ″**Proton Pump Inhibitor: The Double-Sided Action in Gastric Cancer**″

Coauthored by **Moon Kyung Joo, M.D., Ph.D.; Jong-Jae Park; Hoon Jai Chun**

Thank you very much for giving us an opportunity for revision.

A set of comments by the reviewer has proved useful in rewriting this manuscript. We revised this manuscript according to editor's comments point by point. We hope that these changes following the editor's specific suggestions provide improved quality of manuscript and make this paper more suitable for publication. In our response paragraph, we stressed the changes in the revised manuscript as changing the font to **BOLD.**

Thank you!

Sincerely,

Moon Kyung Joo, M.D., Ph.D.

Response points by points

Reviewer #1

The authors have made a good review about the relationship of Proton Pump Inhibitor (PPI) use with occurrence of Gastric Cancer.

1. Please summarize possible mechanisms of long-term PPI use with gastric cancer occurrence in a figure.

Response) We added sentences in figure legends as follows;

PPIs induce hypergastrinemia and hypochlorhydria, which may contribute to ECL cell hyperplasia and proliferation of gastric mucosa. Conversely, PPIs may modify the acidic tumor microenvironment and inhibit vacuolar H^+-ATPase or STAT3 activity in gastric cancer cells.

2. The length of manuscript is redundant. Please shorten the context.

Response) We shortened the length of manuscript. Please refer our revised manuscript.

Reviewer #2

The authors aimed to summarize the data to the role of PPI in gastric carcinogenesis and show potential role of PPI in gastric cancer treatment. From one side the authors deal with arguable topic of PPI and risk of gastric cancer – where the evidence is really yet weak and no conclusion can be made other than before. And second part in similar fashion deals with arguable topic to the value of PPI in cancer treatment- where the evidence is solely based on the mice studies

and in vitro experiments. This makes the review topic so difficult and one sided to my view. The paper could be improved by critical assessment of the evidence and careful statements avoiding direct conclusions.

Major points

1) The title is not clear and may be to offensive. Why should be PPI a sword in gastric cancer? The currently available data are to superficial and not causative. The associational link is rather weak. One study shows some difference another not. To my view PPI are far away to be called a sword in gastric cancer.

Response) We agree with your opinion. According to your suggestion, we change the title as "**Proton Pump Inhibitor: The Dual Role in Gastric Cancer**". Also, we changed "sword" as "role" in abstract and manuscript. Please refer our revised manuscript.

2) Citations-style: the authors cite their own work too frequently unfortunately without taking to account the existing landmark papers. Sometimes the citation even missing!

Response) We agree with your opinion. According to your suggestion, we cited several articles from major journals as follows. Please refer our revised manuscript.

4 Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002; 347(15): 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

6 Yang YX, Metz DC. Safety of proton pump inhibitor exposure. Gastroenterology 2010; 139(4): 1115-1127 [PMID: 20727892 DOI: 10.1053/j.gastro.2010.08.023]

8 Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. Nat Rev Gastroenterol Hepatol 2017; 14(12): 697-710 [PMID: 28930292 DOI: 10.1038/nrgastro.2017.117]

34 Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, Lamers CB, Jansen JB, Dalenback J, Snel P, Nelis GF, Meuwissen SG. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med 1996; 334(16): 1018-1022 [PMID: 8598839 DOI: 10.1056/NEJM199604183341603]

40 Lee AH, Tannock IF. Heterogeneity of intracellular pH and of mechanisms that regulate intracellular pH in populations of cultured cells. Cancer Res 1998; 58(9): 1901-1908 [PMID: 9581831]

42 Chen D, Wu M, Li Y, Chang I, Yuan Q, Ekimyan-Salvo M, Deng P, Yu B, Yu Y, Dong J, Szymanski JM, Ramadoss S, Li J, Wang CY. Targeting BMI1(+) Cancer Stem Cells Overcomes Chemoresistance and Inhibits Metastases in Squamous Cell Carcinoma. Cell Stem Cell 2017; 20(5): 621-634 e626 [PMID: 28285905 PMCID: PMC5419860 DOI: 10.1016/j.stem.2017.02.003]

50 Judd LM, Bredin K, Kalantzis A, Jenkins BJ, Ernst M, Giraud AS. STAT3 activation regulates growth, inflammation, and vascularization in a mouse model of gastric tumorigenesis. Gastroenterology 2006; 131(4): 1073-1085 [PMID: 17030178 DOI: 10.1053/j.gastro.2006.07.018]

63 Bousquet C, Susini C, Melmed S. Inhibitory roles for SHP-1 and SOCS-3 following pituitary proopiomelanocortin induction by leukemia inhibitory factor. J Clin Invest 1999; 104(9): 1277-1285 [PMID: 10545526 PMCID: PMC409825 DOI: 10.1172/JCI7924]

3) English needs improvement (typos, wording etc).

Response) We previously requested proofreading by an English editing company before first submission. We asked once again a native English speaker to proofread the manuscript. Please refer our revised manuscript.

4) Unfortunately, the data regarding PPI and gastric cancer development is not sufficiently critical. There is not clear evidence that proposed hypothesis is true. Also in vitro data are too superficial and the study design is not applicable to draw the conclusion regarding PPI-dependent carcinogenesis.

Response) We agree with your opinion. According to your suggestion, we added the following sentence in "Clinical evidence supporting the association of PPI and development of gastric cancer" section as follows;

(In page 12, the last paragraph) **In summary, several studies have shown a significant relationship between long-term PPI use and the risk of gastric cancer. However, the evidence is far from definitive because of limitations of research design and omission of several major confounding variables. Furthermore, conflicting data also exist. For example, although United States is one of the countries with the most frequent and long-term use of PPI, the incidence of gastric cancer is relatively low[39]. Thus, robust evidence including well-designed, large-scale prospective studies are needed to support the potential association between long-term PPI use and gastric cancer**

In terms of hypothesis for PPI-induced gastric carcinogenesis, we cited a recent pivotal study which demonstrated less relevant carcinogenic effect by PPI rather than *H. pylori* infection, and added a following sentence.

(In page 8 the last paragraph) … **However, this hypothesis is often insufficient to elucidate the mechanism of PPI-induced gastric carcinogenesis. Moreover, a recent pivotal translational study demonstrated that PPI-treated patients showed similar microbial diversity compared with normal subjects while patients with *H. pylori*-induced atrophic gastritis manifested a lower bacterial abundance and diversity. This finding suggested that PPIs do not significantly alter gastric microbiota nor do they contribute significantly to the development of gastric cancer[23].**

5) Premalignant condition and not a lesion is the preferred wording of intestinal metaplasia.

Response) We agree with your opinion. According to your suggestion, we change all "premalignant lesion" as "premalignant condition" in revised manuscript. Please refer it.

6) The authors focus in second part of the paper solely to the in vitro studies while leaving aside what is crucial for translational relevance (any evidence from human studies).

Response) We agree with your opinion. According to your suggestion, we added the following sentence at the end of "Application of PPIs for overcoming chemoresistance" section.

(In page 16) … **However, the lack of human studies and limited clinical relevance represent challenges that need to be addressed before PPIs are used to increase the effectiveness of chemotherapy for actual gastric cancer and improve patient prognosis. Further pre-clinical and clinical studies that are relevant to this hypothesis are needed.**

7) US is one of the countries with the largest use of PPI, however, the gastric cancer incidence

is among the lowest. This discrepancy has not been addressed.

Response) We agree with your opinion. According to your suggestion, we added the following sentence in revised manuscript.

(In page 9 last paragraph) … **Furthermore, conflicting data also exist. For example, although United States is one of the countries with the most frequent and long-term use of PPI, the incidence of gastric cancer is relatively low[39].**

Reviewer #3

This is a very interesting study with regard to the potential contribution of Proton Pump Inhibitor to the development of gastric cancer. In my opinion, in accordance with the final conclusion of the survey, additional research is required in order to verify relevant results. Nevertheless, the article provides current evidence in an attempt to summarize recent literature. Therefore, the manuscript should be accepted for publication in its current form. Several grammatical errors should be corrected.

Response) We previously requested proofreading by an English editing company before first submission. We asked once again a native English speaker to proofread the manuscript. Please refer our revised manuscript.

Reviewer #4

Good and comprehensive review of the topic but English needs to be polished in certain parts as it was difficult to understand. For example, the second sentence in the Introduction: "As technical.....completely resolved"

Response) We previously requested proofreading by an English editing company before first submission. We asked once again a native English speaker to proofread the manuscript. Please refer our revised manuscript.