November 4, 2015

Dear Editors,

We thank the *World Journal of Gastroenterology* for considering our manuscript "Bisphosphonates as potential adjuvants for patients with cancers of the digestive system". We are grateful for the comments and suggestions provided by the reviewers. Please find our responses below.

Reviewer 1: This is a very interesting and comprehensive review. While there is some discussion to be done, I believe this is worth publishing. An issue when we consider bisphosphonates as a candidate of adjuvants for cancer therapy is that it may be carcinogenic in the esophagus. Please add discussions for the followings; 1) Make it clearer the difference of administrative routes of ZA and oral BPs for which there are some reports of increased risk of esophageal cancer. Oral BPs might be carcinogenic because of their direct interaction with esophageal mucosa. ZA is administered intravenously, and irritation of esophageal mucosa may be avoidable.

Response: A sentence discussing the theoretical difference in risk of esophageal cancer associated with oral and IV bisphosphonates has been added to the third paragraph of the section entitled "3.1 Esophagogastric cancers".

2) Please add the reference by Abrahamsen, B., et al., published in N Engl J Med in 2009, which shows reduced risk of esophageal cancer in patients taking BPs.

Response: This reference has been added (#48).

3) Please add the discussion by FDA, http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm264096.htm. And if you add a comment on this, that would be helpful.

Response: This has been added to the end of section entitled "3.1 Esophagogastric cancers" and is listed as reference #54.

Reviewer 2: Ang et al. have written a review covering available evidence that provides a rationale for the use of bisphosphonates (BPs) in in gastrointestinal (GI) malignancies. These drugs are FDA approved for the use of osteoporosis in post-menopausal women and Paget's disease. The first suggestion that BPs may be applicable to cancer was from a randomized clinical trial for adjuvant estrogen suppression therapy in breast cancer that concluded they not only decreased bone loss but also decreased the risk of contralateral breast cancer and improved disease free survival. Subsequent studies in patients with multiple myeloma, lung, and prostate cancer provided evidence for improved oncological outcomes. The authors describe the structure, function, and mechanism of action of this class of drugs. HER- driven cancers are suggested to be appropriate candidates for BP treatment as the drug binds the kinase domain of HER1/2 and inhibits signaling. A subset of GI cancer patients, 15-20%, have epidermal growth factor receptor (EGFR) alterations suggesting they may theoretically be responsive to BPs. Ang et al. mention some but not all side effects associated drug usage. They should include mention of osteonecrosis of the jaw in addition to esophagitis.

Response: We thank the reviewer for pointing this out. We have added a paragraph describing the unique toxicities of bisphosphonates including osteonecrosis of the jaw and atypical femoral fractures to the end of the section entitled "2.0 Bisphosphonate structure, function and mechanism of action".

This review is informative and well written and leads to the correct conclusion that further studies to assess the drug's efficacy in GI cancer is warranted. This is the also the conclusion that Eiken et al. came to recently (in Ther Adv Musculoskel Dis 2015, Vol.7 (4) 160-168- Oral bisphosphonates and colon cancer: an update). They point out that there are no randomized clinical trials that address colon cancer prevention in patients on BPs. They provide however information on six-cohort studies and four-case-control studies that suggest intake of BPs has not shown unchanged or decreased risk of colon cancer and state that BPs should not be used in the clinic for colon cancer. The author's should address that article directly in their review prior to publication.

Response: Thank you for this suggestion. This article is referenced in the final paragraph of the section entitled "3.2 Colorectal carcinoma" and is listed as reference #61.

Reviewer 3: This is an excellent review. I have little to add except for a few edits.

Response: Thank you. All suggested edits have been incorporated into the manuscript.

Reviewer 4: Well written and a good equilibrium basic and clinical studies in the commentaries.

Response: Thank you.

Reviewer 5: This is a comprehensive review and a well written paper. The issue is very intriguing. Only as a suggestion, the Authors could provide a table with an ultra brief dexcription of the studies included, divided into phase-I, phase-II,….randomized and non-randomized trials, number of patients, type, duration of therapy and doses, primary endpoints etc.

Response: A table has been added summarizing all studies referenced in the manuscript, including ongoing and completed prospective studies and observational studies.

Once again, we thank the editors and reviewers for their time and consideration of this manuscript. We hope that the modifications to the manuscript and explanations provided will be found satisfactory.

Best regards,

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