May 15 18, 2016

Professor Lian-Sheng Ma
Editor-in-Chief
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Re: Manuscript NO.: 26606 , "Regional but fatal: intraperitoneal metastasis in gastric cancer"

Dear Professor Ma,

Thank you for your email of May 13, 2016, with the reviewers' comments on our referenced manuscript. We have revised the manuscript in accordance with their comments, as follows:

Reviewer #1:
Comment 1:
In this paper, translational and clinical researches on peritoneal carcinomatosis from gastric cancer were reviewed. Originality is not high, as several review studies and meta-analysis on the same topic are present in literature. Important ongoing trials have been omitted (es. Glehen et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer. 2014 Mar 14;14:183. doi: 10.1186/1471-2407-14-183.) Some English spelling need correction : "lororeginal"

Answer:
As described by the reviewer, there are several meta-analysis in peritoneal carcinomatosis of gastric cancer. However, this review also summarized the potential molecular mechanism of peritoneal metastasis, and individualized treatment of gastric patients that have high risk of peritoneal metastasis. We have added the ongoing trials and corrected some wrong English spelling through the review.

Reviewer #2:
Comment 1:
Why is the intraperitoneal survival rate lower than that of remote metastasis such as liver metastasis? The author did not address on this point in the first section, "Peritoneal metastasis is the most important factor for prognosis in gastric cancer". In addition the author introduced their original data and mentioned "stage IV patients with peritoneal metastasis had shorter survival (7.5 vs. 14 months) and a higher risk of mortality (HR: 2.026, P=0.004)". With what subjects did the author compare the peritoneal metastasis in the stage IV patients?

Answer:
Generally speaking, the median survival time for stage IV gastric cancers is around 9 to 11 months. However, in gastric cancer patients with evidence of macroscopic peritoneal carcinomatosis have a median overall survival of only 3 to 6 months. Patients with intraperitoneal metastasis have shorter survival time due to the poor performance status at the late stage of disease and loss the opportunity for further anticancer treatment.
In our unpublished research, stage IV patients with peritoneal metastasis had shorter survival (7.5 vs. 14 months) and a higher risk of mortality (HR: 2.026, P=0.004). we compared the survival time between patients with peritoneal metastasis and patient with other types of metastasis (supraclavicular lymph nodes and other solid organs, such as liver, lung, bone, and brain, etc.). Our data stand with the same line as some published data that gastric cancer patients with intraperitoneal metastasis have shorter survival time.

Comment 2:
Why did the author think HIPEC better than intraperioneal infusion of docetaxel or paclitaxel? The references for HIPEC were relatively old compared with those of intraperitoneal infusion of anti-

cancer agents. Hence, I think “effective treatments for patients with peritoneal metastasis” may be intraperitoneal infusion and “optional agents for intraperitoneal treatment” HIPEC.

Answer:
We think docetaxel or paclitaxel could be very potential choices for HIPEC as well. We have added some ongoing phase III trials including GASTRICHIP which choose oxaliplatin as the chemotherapeutic antigen for intraperitoneal infusion. We also stated in the review that taxanes were effective drugs for intraperitoneal infusion because they were absorbed through the openings of lymphatic system, such as the milky spots and the stomata which are important sites for the formation of peritoneal dissemination.

Comment 3:
The last section of manuscript is “selected population for intraperitoneal chemotherapy”, however, this is like a subject of study, so this section is recommended to locate after the section of “molecular mechanisms of peritoneal metastasis”.

Answer:
We have modified our review according to the reviewer’s comments.

No comments from Review #3 and #4.

Thank you for your consideration of our manuscript.

Sincerely,

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