Round-1

April 12, 2021

Drs. Jia-Ping Yan and Lian-Sheng Ma, Editors
World Journal of Gastrointestinal Oncology

Dear Drs. Yan and Ma,

Thank you for your thorough review of our manuscript "Targeting of elevated cell surface phosphatidylserine with SapC-DOPS nanodrug as individual or combination therapy for pancreatic cancer". Below you will find our responses and revisions to the thoughtful and constructive suggestions provided to us from the peer reviewers and editorial staff. The changes in the manuscript are in red font for ease of identification.

Peer-Review

Review #1

Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision

Specific Comments to Authors: Very interesting and well written review. It clearly demonstrates possible benefits of SapS-DPOS not only from a therapeutic stand point but also as a possible imaging agent. Its synergist effect with current chemotherapy agents and even in combination with radiation on tumor cells makes this a drug a very promising new addition to currently available medications. I would like to know if there are any studies regarding combination with mFOLFIRINOX as it is first line treatment in fit patients. As you say in your introduction gemcitabine is a first line drug but not "generally the first line", particularly in monotherapy. Also, please review Table 1 as per AJCC 8th edition (please refer to attachment). Congratulations.

I would like to know if there are any studies regarding combination with mFOLFIRINOX as it is first line treatment in fit patients. As you say in your introduction gemcitabine is a first line drug but not "generally the first line", particularly in monotherapy.

Thank you for this comment. We added two references to discuss mFOLFIRINOX and GEM/Abraxane use. We have conducted some studies (including in vivo) with GEM/Abraxane and SapC-DOPS, which were included in the original review. However, at this time we have not studied mFOLFIRINOX with SapC-DOPS.

We also changed the wording on page 4 from "generally the first line" to "Gemcitabine (GEM, Gemzar) is a first line drug for advanced pancreatic cancer." GEM is still used on patients who cannot tolerate mFOLFIRINOX. We also added a paragraph on page 5 discussing a trial for mFOLFIRINOX and a trial comparing GEM/Abraxane to FOLFIRINOX. "In a recent study, adjuvant therapy with a modified FOLFIRINOX protocol led to significantly longer disease-free survival than with GEM among patients with resected PDAC (21.6 vs. 12.8 months), but had a higher incidence of adverse events of grade 3 or 4 (75.9% vs 52.9%). In addition, a retrospective study, Perri, et al. showed that patients with localized PDAC who received FOLFIRINOX or the combination of GEM and Abraxane as their first line of therapy, FOLFIRINOX was associated with a higher rate of RECIST partial response, allowing subsequent pancreatectomy, than GEM/Abraxane but the overall survival rates were similar (20 vs. 21 months). However, the patients treated with FOLFIRINOX were significantly younger (61 vs. 71 years)."

Also, please review Table 1 as per AJCC 8th edition (please refer to attachment).

We have changed the Table to adhere to the AJCC 8th edition.

Reviewer #2:

Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Specific Comments to Authors: Comments to the Author In your review, you describe the mechanisms and efficacy of SapC-DOPS, a novel phosphatidylserine (PS) biomarker targeted nanodrug, alone and in combination with other treatment modalities such as gemcitabine (GEM), Abraxane and radiation for the treatment of pancreatic ductal adenocarcinoma (PDAC) tumors in vivo, which has not been reviewed in the literature. Your reference documentation is very comprehensive and the review concludes almost all conditions that may have something to do with SapC-DOPS. I can imagine how much work you have done for this professional review. I recommend that you give a final polish to your writing to keep your message as concise as possible. For example, there's too much in the introduction and current therapy sections. I really appreciate your great work and it's my great honor to read this paper.

Thank you for your feedback regarding introduction section. Although we understand the reviewer's concern that the chemotherapeutic agents are not the focus of our review we attempted to give a broad background for the treatment of pancreatic cancer. Our continuing interest is to investigate the combination of SapC-DOPS with other treatments.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: As early as 2011, the author proposed a novel nanosome SapC-DOPS . This substance can inhibit the proliferation of tumor cells and enhance the toxicity of gemcitabine, but the effect in vivo is not clear, and additional in vivo tests are needed.

We are perplexed by this comment as we described a number of in vivo studies in the manuscript on pages 7 and 8. "To advance these studies, human PANC-1 or MiaPaCa-2 cells were implanted subcutaneously in nude mice then the mice were treated every two to three days with various doses of SapC-DOPS. Our results demonstrated a dose-dependent inhibition of pancreatic tumor growth by SapC-DOPS. To investigate a more pathologically important model, mice were implanted with cfPac-1 cells orthotopically into the pancreata. In these mice, SapC-DOPS dramatically prolonged survival; tumor-bearing control mice all died within 170 days but 67% of SapC-DOPS-treated mice survived until they were euthanized at day 260 and none of the surviving mice harbored any detectable tumor. Notably, a metastatic tumor appeared in the lung of one mouse (Fig. 2A) and this lesion was targeted by SapC-DOPS[24].

As mentioned, GEM provides only marginal benefit to patients so we assessed the therapeutic benefits of combining GEM with SapC-DOPS. For these studies[29] we first, treated MiaPaCa-2 cells with SapC-DOPS (48 h) and GEM (24 h) alone as well as a combination of SapC-DOPS with GEM. These data demonstrated that the combination of SapC-DOPS and GEM had a significantly greater anti-tumor effect than either treatment alone. Interestingly, low dose GEM treatment elevates surface PS on cancer cells lines within 48 hours without killing the cells, although this may be an early, aborted apoptotic response. We then implanted the pancreatic cancer cell line, p53.2.1.1, subcutaneously into c57Bl/6J mice[29]. We used suboptimal concentrations of both GEM and SapC-DOPS and only treated on days 1 and 4 post implantation to examine the combination effects. Both GEM and SapC-DOPS alone reduced tumor sizes by about 50% but the combination reached 90%. A similar experiment was conducted using subcutaneous mouse 4580P cells in c57Bl/6J mice with GEM/Abraxane and SapC-DOPS with similar results. To ascertain whether the combination could improve survival, we injected mice orthotopically with p53.2.1.1 cells and then administered saline, GEM, SapC-DOPS or the combination. All the control mice died within 29 days. The mice receiving the combination treatment lived substantially longer with one mouse being euthanized tumor-free on day 50. The mice receiving suboptimal concentrations of either GEM or SapC-DOPS alone lived for an intermediate duration. In all of these experiments SapC-DOPS was introduced shortly after the injection of the GEM or GEM/Abraxane."

In addition, we mentioned that SapC-DOPS has completed a Phase I clinical trial (and is now in Phase II). To get this far, the FDA apparently feels comfortable with the in vivo studies we have conducted.

Editorial Office Review

(1) Science editor: 1 Scientific quality: The manuscript describes a minireview of the phosphatidylserine-selective therapies for pancreatic cancer. The topic is within the scope of the WJGO.

(1) Classification: Grade B, Grade B and Grade C;

(2) Summary of the Peer-Review Report: Very interesting and well written review. It clearly demonstrates possible benefits of SapS-DPOS not only from a therapeutic stand point but also as a possible imaging agent. This substance can inhibit the proliferation of tumor cells and enhance the toxicity of gemcitabine, but the effect in vivo is not clear, and additional in vivo tests are needed. The questions raised by the reviewers should be answered; and

(3) Format: There is 1 table and 4 figures.

(4) References: A total of 45 references are cited, including 8 references published in the last 3 years;

(5) Self-cited references: There are 15 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e., those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated.

We removed two self-citations and added two other references (mentioned above) but we are still over 10% self-citations. However, the primary topic of this review is SapC-DOPS, which was developed by one of us (Xiaoyang Qi). Thus, all of the research on this modality has been done by his group so we are not sure how we can reduce the percentage of self-citations without severely limiting the discussion of the drug. In fact, Reviewer 1 comments that we should shorten the background and discussion of other pancreatic cancer drugs to enhance the emphases on SapC-DOPS (**"I recommend that you give a final polish to your writing to keep your message as concise as possible. For example, there's too much in the introduction and current therapy sections."**). This would obviously increase the self-citation rate.

(2) Language evaluation: Classification: Grade A, Grade B and Grade B. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

We have provided the Conflict of Interest forms.

No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was performed with 6 financial supports. The topic has not previously been

published in the WJGO. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions;

We have addressed the Authors' Contributions on page 12. "H. Davis and X. Qi conceptualized the review. A. Kaynak helped generate the figures. All authors made major contributions to the review's literature search and contributed to drafting the manuscript. All authors contributed to some or all of the original studies discussed in this review. All authors provided critical review and approved the final manuscript before submission."

(2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Approved grant application form(s) have been uploaded.

(3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

The original figures in PowerPoint have now been added and all graphs or arrows or text portions can be reprocessed by the editor.

(4) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights.

All of the figures are original to this review and do not need approval from any other journal.

(5) Re-Review: Required.

(6) Recommendation: Conditionally accepted.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Thank you for your comment. The title has been changed to "Targeting of elevated cell surface phosphatidylserine with SapC-DOPS nanodrug as individual or combination therapy for pancreatic cancer."

Again, thank you for your consideration of our review. Although we feel that some of the changes requested are not feasible, we believe that the reviewers' comments have allowed us to strengthen the manuscript and we hope that our changes are acceptable.

Sincerely,

Xiaoyang Qi, PhD
Professor, Hematology-Oncology
University of Cincinnati

Round-2

Drs. Jia-Ping Yan and Lian-Sheng Ma,
Editors
World Journal of Gastrointestinal Oncology
Dear Drs. Yan and Ma,

Reviewer
Thank you for the changes. You can find attached a suggestion for the AJCC prognostic groups as there are still some minor details that are not in accordance with the 8th edition. Congratulations.

Thank you for your re-review of our manuscript “Targeting of elevated cell surface phosphatidylserine with SapC-DOPS nanodrug as a novel individual or combination therapy for pancreatic cancer”. We have made the changes to Table 1 as suggested by Reviewer #1. Peer-Review Review #1 Thank you for the changes. You can find attached a suggestion for the AJCC prognostic groups as there are still some minor details that are not in accordance with the 8th edition. Congratulations. Thank you for your suggestion. We have made the changes to Table 1.

Sincerely,

Xiaoyang Qi,
PhD Professor, Hematology-Oncology