Facultad de Estudios Superiores
IZTACALA

Tlalnepantla, Estado de México, November 2, 2022

Li Ma
Science Editor, Editorial Office Director,
Editor-in-Chief
Baishideng Publishing Group Inc

Dear Dr Ma:

Thank you for your letter and referee comments dated on October 20th, 2022, concerning our manuscript number 80348, originally entitled “Are Immunosuppression and Conventional Chemotherapy the key to increasing immunotherapy efficacy during colorectal cancer development?” coauthored by Jonadab Efraín Olguín, Mónica G. Mendoza-Rodríguez, C. Ángel Sánchez-Barrera and Luis I. Terrazas. The comments by the 2 reviewers were extremely useful and most appropriate. We have gone through their suggestions and revised the manuscript by incorporating additional changes as follows:

Point-by-Point comments:

To both reviewers, we want to thank all of your comments that we are sure will improve our manuscript.

Reviewer #1:
Specific Comments to Authors:

Q.1 This is an interesting review article on potential therapies used for treating CRC. While some of the information given in the review is novel other facts regarding treatment are well known. At times English language needed correction particularly in the statement and I quote: 'In another study in Australasian and Canadian populations with asymptomatic patients using the same chemotherapy regimen, NON-DIFFERENCES were reported between early and delayed chemotherapy use until symptoms...[42]. Please use 'no difference'.

R. Thank you for your nice comments. We have incorporated more recent findings and reduced the traditional knowledge. Regarding grammar troubles, we also submitted the document to a professional English language editing company.

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Q.2. The NRAS gene is associated with malignant proliferation and metastases of CRC. The authors should refer to a recent meta-analysis which showed that NRAS could predict the poor prognosis for CRC (Yue Hu et al., 2018). Please include this reference and include some more recent references.

R. We appreciate your review very much. Hu et al. 2018 and additional recent references that support the statement mentioned above have been included.

Q.3. Please define FOLFIRI in a list of abbreviations. Please include all abbreviations in a list before the references.

R. Thank you for this comment. We included a list of abbreviations before the references section, and FOLFIRI definition was included.

Q.4. There were no diagramatic representations of the text. Flow diagrams will help in this regard, especially when explaining the pathways of tumorigenesis. The authors mention ICI avelumab monotherapy and darvalumab in microsatellite-instability high/mismatch repair-deficient metastatic CRC patients, and an improvement in progression-free survival. What is the mechanism of action of these monotherapies? A diagram may also be used to explain the mechanism.

R. We agree with this comment, and based on the literature, we depicted the classical ICI mechanism of action using either durvalumab or avelumab blocking the interaction of PD1/PDL1. In fact, as we mentioned in the text, anti-PDL1 antibodies have superior efficiency in blocking PD1/PDL1 signaling (reference 72 in text, doi.org/10.1038/s41598-019-47910-1). Once anti-PDL1 antibody avoids the interaction between either tumoral cells or myeloid suppressor cells expressing PDL1 molecule, with T cells expressing PD1, the latter return from the state of anergy in which they were found to exert their effector function, either by producing cytokines (T-CD4^{+}) or by exerting cytotoxicity (T-CD8^{+}), favoring the reduction of the tumor burden. We think that this new Figure 3, enriched with the suggestions of Reviewer 1, generates more didactic and clearer information for the review.

Q.5. The advantages of using combined immunotherapy egs: ipilimumab plus nivolumab before surgery is well explained. How were the lack of signs of cancer after surgery assessed?

R. Thank you for this observation. Johnson and colleagues (ref 89 in text, doi.10.1200/jco.2020.38.4_suppl.152) evaluated the reduction of signs of cancer

by detecting carcinoembryonic antigen, where they found lower levels after this treatment. They also evaluated by flow cytometry the expression of PD1, Tim3 and LAG3 molecules in $CD8^+$ cells, which dropped after this combinatory treatment.

Reviewer #2:
Specific Comments to Authors:

Q1. The review is too long. Q2 The title is not suitable,

R. Thank you for your review and opinion. We have tried to shortener this review, mainly in the conclusion section but also, we tried to accomplish the comments of reviewer 1, who asked for more details in some parts of the text. In addition, we have modified the title as you suggested: “Is the combination of immunotherapy with conventional chemotherapy the key to increasing the efficacy of colorectal cancer treatment?”. We think that this new title better reflects the review’s content.

Q3. The authors present the efficacy of conventional chemotherapy, immunotherapy and immunosuppression of CRC in separate subchapters. They preset in only 1 page the studies regarding the immunotherapy plus chemotherapy for treatment of CRC.

R. Thank you for this observation. Over the years, the literature has focused mainly on the effect of chemotherapy on oncological pathologies, while separately and more recently, the effect of combined therapy (combination of ICIs or chemotherapies) has been studied. On the other hand, the study of immunotherapy in CRC is very recent. There are few studies (12 in total) where immunotherapy and chemotherapy were combined for CRC treatment, which is the reason to present only 1 page in this regard. We made emphasis on the fact that some research is under development and that is necessary to develop new studies.

Q4. In my opinion they should give up the following subchapters: Conventional treatments of colon cancer and mechanisms of action from a genetic perspective. The 5-fluorouracil mechanism of action. Use chemotherapeutic strategies for colon cancer treatment; which is the right drug? Chemoresistance to treatment in colon cancer. The authors should focus on the topic.

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Thank you for this observation. We considered the necessity to improve the landscape of conventional chemotherapies and mechanisms related to chemosensitivity and resistance, which may provide the basis for immune therapy. The immune population cells in the cancer microenvironment could be regulated by conventional chemotherapeutics such as 5-FU (doi. 10.1158/0008-5472.CAN-09-3690). The role of chemotherapies of CRC and their effects on immune checkpoint expression are controversial, and their uses as single therapies have not been as beneficial as expected. Thus, we used the subchapters suggested to explain only the chemotherapy section. The invitation received in June 2022 to participate with a review article in WJGO has the topic: “Challenges to addressing the unmet medical need for immunotherapy targeting cold colorectal cancer”. The second part of this review focused on the topic for the use of immunotherapy as a target of CRC. From our perspective, it is necessary to include both the entire section of classical immunotherapy and the new immunotherapy proposals to explain the topic reflected in the new title.

Q. The conclusions are too long. There are bibliographic indices that are missing.

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R. Regarding this comment, the conclusion section was restructured and shortened. We apologize for the missing references. We have carefully checked out this and added the missing references.

We hope you find this manuscript interesting and valuable for its publication in your prestigious Journal, World Journal of Gastrointestinal Oncology.

Sincerely yours,

Dr. Luis I. Terrazas