Point by point letter

Manuscript number: 75091, Minireviews
Title: Combination approaches in hepatocellular carcinoma: how systemic treatment can benefit candidates to locoregional modalities
Authors: Leonardo G Da Fonseca, and Raphael LC Araujo

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Editorial Office
World Journal of Gastroenterology

Dear Editor,

Thank you for the positive feedback regarding our minireview. We have taken our time to address all the points raised by the reviewers and we are sure that they significantly improved the quality of the manuscript.

In the following pages, we provide a point-by-point response to each reviewers´ comment and describe what amendments have been made to the manuscript text. Moreover, we highlighted in Yellow in the text all changes that were made. We hope this version will be found acceptable for publication in the World Journal of Gastroenterology.

Best regards,

Raphael LC Araujo and Leonardo G da Fonseca

Point by point response

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Hepatocellular carcinoma (HCC) is the fourth cause of cancer-related mortality worldwide, and a wide range of treatment options for HCC are selected based on some clinical standards. Here the authors summarized the current landscape of systemic and locoregional treatments for HCC and showed evidence to support combination approaches and future perspectives.

Response: We appreciate your review and feedback.

1, All the figures in this manuscript are too abscure to read.

Response: We improved both the definition and quality of figures, as well as adjusted the font size.

2, The conclusion part need to polish, to highlight the future of this field and give more suggestions and predictions.

Response: We have polished the conclusion part, highlitghting future and perscpectives, as follows: *"The most promising ongoing trials approach the combination of TACE and immunotherapy, with the aim to significantly delay time-to-progression and, hopefully, increase cure rates for patients who achieve complete response with locoregional treatment. Similarly, trials that test adjuvant immunotherapy after ablation may increase cure rates by reducing the risk of recurrence and even de novo tumors. It likely that biomarkers and subsets of clinical features will emerge from these trials and will support the selection of patients that will derive more benefit from combination approaches."*

3, Some mistakes in this manuscript need to be improved, i.e. "after tumor ablation and the the use immunotherapy is encouraging.", additional "the" need to remove.

Response: Thanks for pointing that. We have made extensive review to capture and improve mistakes.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The submitted mini-review: combination approaches in hepatocellular carcinoma: how systemic treatment can benefit candidates to locoregional modalities, presents an interesting look into the available combinatory therapeutic approaches for HCC vs monotherapies like VEGFR-drugs. The following few points are raised:

-Include a section in this review showing all important abbreviations.

Response: We appreciate you review and feedback. In this reviewed version, we have added a section with abbreviations.

-There are number of paragraphs or sentences that need to be connected

Response: In this reviewed version, we have made an effort trying to make some parts more connected and linear.

-In the following paragraph: (Combination of ablative and systemic treatment: rationale and current evidence): Give more examples for the novel markers in: (Novel markers such as genetic signatures, circulating microRNA, and circulating tumor cells have also been shown to predict the risk of recurrence).

Response: Thanks for the suggestion, we added more novel potential markers in the sentence, as follows: “Novel markers such as genetic signatures, circulating microRNA, circulating non-coding RNA, circulating cell-free DNA, gut microbiota, and circulating tumor cells have also been shown to predict the risk of recurrence”

-Page 13: Guidelines recommend that patients patients who present progression with infiltrative -Give example of score(s) in page 13: (The decision to declare TACE failure and switch to systemic treatment is heterogenous in different parts of the world and many scores has been proposed to help in this decision, although some of them still require further validation).

Response: We appreciate the comment. We have given examples of these scores, such as ART score and HAP score: “For example, the hepatoma-arterial embolization (HAP) score includes albumin, AFP, bilirubin and tumor diameter and was concepted to predict prognosis before the first TACE in an heterogeneous cohort with around 30% of BCLC-C patients [63]. The Assessment for Retreatment with TACE (ART) score was designed to evaluate benefit of a 2nd TACE and consider Child-Pugh score, AST and tumor response after the first TACE. The ART was originally developed in a cohort that included around 20% of patients with impaired liver function (Child-Pugh B8 or more)[65] “.

-Page 14: rewrite the following: (It has been demonstrated an increased intratumoral microvessel density and VEGF expression in residual surviving cancerous tissue after TACE).

Response: We have rewritten the following sentence to make it clearer: “The rational for testing these combinations comes from the demonstration of increased intratumoral microvessel density and VEGF expression in residual tumor after TACE, suggesting that TACE may stimulate tumor angiogenesis.”

-Table 1: briefly describe and comment on the RECIST % of the different studies.

Response: Thanks for raising this important point. We added a setence in this regard: “These preliminary results suggested that combinations may yield response rates of more than 20% according to RECIST criteria, what seems to compare favorably to the rates with multikinase inhibitors. However, it is important to point some limitations of early phase trials. Firstly, non-comparative trials are not adequate to draw definitive conclusions. Besides, response rate is not a surrogate marker for survival benefit in HCC, even more considering that RECIST may not capture the spectrum and patterns of progression and response in patients under immunotherapy.”

-Figure 1: The figure is blurred, make it clearer

Response: We improved both the definition and quality of figures, as well as adjusted the font size.

-Figure 2: define the first part of the figure on the left (hepatocells,,,)

Response: Thanks for you suggestion. We added tags to clarify the meaning of each part of the figure 2.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Emerging data indicate that locoregional treatments may induce tumor microenvironment changes, such as hyperexpression of growth factors, release of tumor antigens, infiltration of cytotoxic lymphocytes and modulation of adaptative and innate immune response. Thess events show that the use of systemic agents in combination with local therapy is very important. This review describes the current landscape of systemic and local treatments for HCC, and provide evidences to support combination approaches and future perspectives.

Response: Thank you for the positive feedback, we agree with the importance of the ongoing and future data about combination approaches.

(1) Science editor:

The author summarizes the current situation of systematic and local treatment of liver cancer and shows the evidence supporting the combined treatment and future prospects. The manuscript is well written and has a certain value for the current research. Figure legend should be supplemented completely. In addition, figure 1 is unclear. The format of the table should be a three-line table.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Response: We trully appreciate your view. We have improved figure legend, as well as improved quality of figure 1. Additionaly, we have adjusted tables.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, 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. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open

multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden.

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Response: We appreciate your points. We have made these adjustments.