October 1, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format **"Manuscript 02766749-Cuestas et al.doc"**

Title: Hepatocellular carcinoma and multidrug resistance: past, present and new challenges for therapy improvement.

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Name of Journal: *World Journal of Pharmacology*

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The manuscript has been improved according to the suggestions of reviewers:

First of all, the authors would like to thank the thorough revision performed by all of you.

To Reviewer # 00504311

1. The suggested references regarding brivanib in recent clinical trials were added both within the text (Page 29, lines 19- 23) and within the "References" Section (#109 & #110).

To Reviewer # 01557574

1. No comments to be added.

To Reviewer # 02445626

All your contributions have been incorporated within the text.

1. The title was amended, as suggested, paying more attention to improved treatments, rather than conventional therapies (as also shown within the text in the "Perspectives" Section). Accordingly, 20 new references were depicted within the new version of the manuscript.

2. Clarification was made in the paragraph "Surgical resection and orthotopic liver transplantation are considered the treatment of choice", as shown in Page 4, lines 19-20.

3. The paragraph **"**A clinical investigation indicates that none of the adjuvant therapies is particularly effective in the treatment of HCC after surgery [16]." was added as suggested, in Page 5, lines 5-7.

4. Paragraph regarding the promising use of sorafenib was amended as suggested, in Page 5, lines 20-25. "Up to now, no succesful systemic chemotherapy for patients with advanced and unresectable HCC is available. However, on November 16, 2007, the Federal Drug Administration (FDA; USA) had approved sorafenib tosylate (Nexavar® tablets, made by Bayer Pharmaceuticals Corp.), as "*a small molecule Raf kinase and VEGF receptor kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC)*". Unfortunately, this promising treatment has demonstrated limited survival benefits with very low response rates [24, 25]."

5. The redundant paragraph in Page 6 was deleted, and clarification regarding anti-sense therapy was introduced.

6. A reference was provided, as requested, in Page 7, line 18: "[10]".

7. Two references as well as their significance were included in Page 7, lines 14-17: "Moreover, several studies demonstrated disappointing results, showing that TACE enhances intrahepatic and extrahepatic metastases, and even reduce survival[36] . Accordingly, anti-angiogenic therapy enhances the efficacy of transcatheter arterial embolization for HCC hepatocellular carcinomas [37]."

8. The first paragraph from the "Hormonal therapy" Section was deleted, as suggested.

9. The more recent reference regarding systemic chemotherapy was added in Page 12, lines 19-21, as suggested: "In a recent clinical trial involving a large number of HCC patients, systemic administration of doxorubicin has provided a very low response rate (4%) [64]".

10. A requested paragraph regarding improved immunotherapies, is included within the "Perspectives" Section.

11. "Molecular target therapy" Section: 1 Table and 2 figures were included, as suggested, to clarify

the main pathways and drugs related to them.

12. Two requested references and the corresponding paragraphs were added in Pages 17 and 18, as references #90 and #99.

13. "Other Drugs" Section. A reference was added at the end of the paragraph, as requested: [149].

To Reviewer # 00503849

Most of your contributions have been incorporated within the text. However, it should be stressed that the last sentence in your "Reviewer´s comments" Section, appeared to be trimmed. Therefore, the authors could only answer your previous comments / requests.

1. The title was amended, as suggested, paying more attention to improved treatments, rather than conventional therapies (as also shown within the text in the "Perspectives" Section; see below).

2. As requested, a Table and 5 Figures were included along the text, to facilitate the understanding of the article.

3. All references were reviewed, and 20 new cites are provided (most of them from the very last years).

4. Clarification was made in the paragraph "Surgical resection and orthotopic liver transplantation are considered the treatment of choice", as shown in page 4, lines 19-20.

5. Reference 11 (Page 4 lines 24-25) was replaced by a new one, as requested: "Furthermore, about 17-69% of patients suffer from recurrence, thus limiting their long-term survival at 5 years postoperatively [11]."

6. Page 5: The statement regarding references "17-19" (previously, "16, 18") was amended, as requested.

7. Reference "21" (currently "22") was placed properly.

8. The sentence requested to be revised, was amended as follows (Page 7, lines 6-8): "The strict Milan criteria for transplantation, in addition to limitations of donor availability, have thus encouraged researchers to investigate other modalities of treatment that might overcome the drawback of transplantation or surgical resection [30]."

9. "Percutaneous treatment" Section (Page 7, lines 15-16). The sentence was amended, according to your suggestion: "Thermal ablation consists of destroying tumor cells by cryoablation or by heat

using lasers, high intensity focused ultrasound, microwaves or radiotherapy."

10. Page 7, lines 16-18: The sentence was amended, as requested: "Chemical ablation consists on cancer cells destruction by injecting chemicals -e.g. ethanol / acetic acid- introduced into the tumor mass by means of a very fine needle [10].

11. The suggested paragraph regarding "Hepasphere or DC bead for TACE" was not included in the text, since the main focus of this review is not directed to TACE and in order to avoid an imbalance of the already described topics.

12. Median overall survival (MOS) of patients from Hilgard *et al* study (Hepatology, 2010; reference #50) was 16.4 mo and a new updated reference (#51) showing a MOS of 18 mo was included as well (Page 9, lines 29-30).

In order to answer your question regarding the sort of patients included, we would like to mentioned the following inclusion criteria.

In the first study (Ref. 50), 108 consecutive patients with advanced HCC and liver cirrhosis were included. The major clinical features allowing Y-90 treatment and therefore inclusion into this observational study were nonresectability of HCC and BCLC C tumor stage. Patients with BCLC A and B were also included if they were not eligible for selective TACE. Additional inclusion criteria were adequate hypervascularity (concentration and consecutive "blush" of contrast agent in the arterial phase of CT and/or contrast-enhanced ultrasound), a liver function with a Child-Turcotte-Pugh (CTP) score ≤7 points, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

In the second study (Ref #51), patients presenting with liver cirrhosis and Child–Pugh category C were not offered radioembolization. Among the patients with HCC, 6 presented with Child–Pugh stage A (5–6 points) and 2 with stage B (7 points). Inclusion criteria for all patients at initial or repeated radioembolizations comprised an East Coast Oncology Group (ECOG) performance status of 0–2, a Karnofsky index above 70%, a platelet count above 50,000, a prothrombin time of at least 50%, and bilirubin below 30 μmol/L. Controlled ascites and partial portal-vein occlusion were not exclusion criteria.

13. "External beam radiotherapy (EBRT) / stereotatic body ratiation therapy (SBRT)" distribution within the text. As mentioned in the original manuscript, EBRT encompasses SBRT, which is described below, separately.

14. Patients receiving SBRT therapy in the study by Choi et al (Jpn J Clin Oncol, 2006) included

were those who fulfill the following conditions: 1) not showing extrahepatic metastasis; 2) belonging to a group lower than B on Child´s classification; 3) ECOG score <2; 4) no previous experience of radiation treatment; and 5) having a single lesion.

15. "Hormonal Therapy" Section. As requested, the text was trimmed.

16. Octreotide: a (previously mentioned) reference was added at the end of the pointed paragraph (Page 12, lines 8-11).

17. Statement about doxorubicin median overall survival. In Page 12, lines 19-21, a newer reference replaces the previous one, showing a 4% rate (instead of 20%).

To Reviewer # 02444768

1. Spelling errors have been amended, as requested.

2. A Table and 5 Figures were added to facilitate the comprehension.

3. Balance between "Molecular target therapy" *vs* "DDS" sections. Although the authors agree with the reviewer´s view on the different length of these sections, we could hardly pose equivalent amount of data, due to the very recent development of the latter, specifically in the hepatocellular carcinoma field.

Thank you again for publishing our manuscript in the *World Journal of Pharmacology.*

Sincerely yours,

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