Format for ANSWERING REVIEWERS

Dear Editor,

please find enclosed MS#: WJH 14-881 entitled

"Advanced HCC and sorafenib: Diagnosis, Indications, Clinical and Radiological Follow-Up"

revised according to the suggestions by the reviewer.

As requested, in the annotated copy, all changes/additions are blue typed (and the number of Reviewers 'concern / suggestion is reported). We have also enclosed, below, a point-by-point letter answering all questions raised by the reviewers.

We do hope you and the reviewers will find the revised version of our paper suitable for publication in the WJH.

Sincerely yours, with by best regards

Florence, December 27, 2014 Stefano Colagrande, MD

Reviewer 1: no concerns, no questions

Reviewer 2: no concerns, no questions

Reviewer 3:

Colagrande et al. submitted the manuscript entitled "Advanced HCC and sorafenib: diagnosis, indications, clinical and radiological follow-up" for peer review. The paper is an interesting review on the current utility of sorafenib in the treatment of advanced hepatocellular carcinoma. The manuscript provides also insights on the intrinsic clinical problems and limitations of sorafenib, and summarizes possible future improvements in its application. Despite the review is well structured, a number of minor issues need to be addressed and are listed below:

3-1) The style of the manuscript appears too discursive, especially in the first two paragraphs. In order to keep the reader focused on the main messages of each section, the Authors should present data in a concise way and possibly give data about the clinical studies mentioned.

Yes, the whole ms. has been reworded.

3-2) In the section "Diagnosis, staging and treatment allocation" the Authors state "… some others consider TACE not safe in patients with so advanced disease and recommend this treatment only in patients with Child-Pugh A cirrhosis and segmental portal vein thrombosis". The use of TACE in the presence of neoplastic thrombi in the portal branches is controversial. The Authors should add more data to support their assumption, since the reference mentioned is too vague.

As requested, the following sentences has been added in order to clarify this point:
"In fact Chung et al recently published a work including 125 patients with main portal vein thrombosis (83 treated with TACE and 42 with the best supportive care) where a better outcome of the patients in TACE group has been shown, with an OS of 5.6 and 2.2 months respectively for TACE and control group. In this work no procedure related deaths happened (19)
Conversely some other authors consider TACE not safe in patients with so advanced disease and recommend this treatment only in patients with Child-Pugh A cirrhosis and segmental portal vein thrombosis (21). This theory probably finds the basis in the ischemic hepatic damage produced by TACE, with secondary decrease in liver function (19)"

3-3) In the paragraph "Sorafenib treatment" the Authors state "this drug showed a significant improvement …, but the number of partial responses in the treatment group was low (7 out of 299)". This assumption may result difficult to understand without showing the other results according to the RECIST criteria of the study mentioned. Moreover the proportion of the patient responding to sorafenib should be clearly stated.

We have added, as requested, the following sentence with more details about the other results according to RECIST in the SHARP study:
"In all groups the number of partial responses was low: 7 out of 299 for the treatment group (2%) and 2 out of 303 (1%) for placebo group. Conversely the majority of patients presented stable disease: 211 out of 299 (71%) in treatment group and 204 out of 303 (67%) in placebo group. No complete responses have been found.(ref SHARP 17)"

3-4) The Authors should add references to the Table 1 and Table 2.

The following references have been added: " ref n° 3-19-20-21-22-26-27-28-29 in table 1" and ref n° 5-17-18-37-97-98-99-100-101-103 in table 2"

3-5) In order to help the reader in the interpretation of the radiological images, the Authors should provide the legends of Figure 2 and Figure 3.

The legends have been improved and detailed.

3-6) The Authors should make sure that each abbreviation is expanded at first use in the manuscript and in the abstract.

See point 4-1

3-7) The manuscript should be revised for English grammar errors. Moreover, the authors should avoid contractions of verbs and the use of adverbs (e.g. actually) that are more appropriate for spoken language.

Yes, the revision has been done

3-8) The list of Authors and their affiliations should be indicated in the paper. The manuscript should be typed in 1.5 line spacing.

Yes, we have provided a Full title page and we have corrected the line spacing.

Reviewer 4:

Comments to the author: The given review is summarizing current information about therapy of advanced hepatocellular carcinoma (HCC) with a special focus on sorafenib treatment. The review is subdivided into 7 parts (Introduction; diagnosis, staging and treatment allocation; sorafenib treatment; biochemical response evaluation parameters; imaging response evaluation parameters; sorafenib failure and second-line therapies; conclusion). However, several points need to be addressed prior to publication.

4-1) The abstract needs attention: Some words e.g. HCC has to be announced as hepatocellular carcinomas, trans-arterial radio embolization as TACE, AE as adverse events. The diagnosis of HCC is also defined by pathological parameters.

Done

4-2) The key words have to be ordered alphabetical.

Done

4-3) The introduction is not discussing the importance of the underlying liver diseases.

The following sentences has been added:
"In fact, at least 80-90% of patients with HCC present an underlying liver cirrhosis, that represent the major risk factor for HCC irrespective of its etiology (HBV or HCV infection, alcohol, non-alcoholic steatohepatitis representing the most frequently involved) [Colombo M, de Franchis R, Del Ninno E, et al. *Hepatocellular carcinoma in Italian patients with cirrhosis.* N Engl J Med 1991; 325 (10): 675-680 – i.e. ref 3, new]. The possible related loss of liver function assumes a critical role when a treatment strategy has to be chosen. As a result, the management of HCC often includes a proper management of two different diseases: HCC and liver cirrhosis."

4-4) Why did the authors focus on the American HCC guidelines and the Japanese guidelines, but not on other international recommendations.

Actually the manuscript contains references to international guidelines (American, European and Japanese) that are currently used in clinical practice. The American and Japanese guidelines are mentioned in the manuscript in

order to show the radiological improvement in the diagnosis of HCC that has been reached during the last decade.

4-5) According to the recommendation of Bayer, Sorafenib treatment is not restricted to Child Pugh A patients, this is a very important point and has to be discussed in a proper way.

We modified the sentence at page 6, as follows: "According to technical schedule sorafenib should be orally administered at 800 mg/die (400 mg twice a day)."
We added the following sentences at page 7, line 10: "As the liver function can be compromised by the drug, the use of sorafenib in patients with a Child Pugh score equal or greater than B7 is still controversial. In fact, the progression of cirrhosis more than HCC could lead to a discontinuation of the therapy in this subset. In general, data published so far suggest the feasibility of the therapy in this population, with a particular attention due to a greater probability to develop AE and a poorer clinical outcome in general. However, Child Pugh B is not to be managed as a unique class of patients. In fact, as well known, the prognosis largely varies stratifying the Child Pugh B patients according to their individual score (B7, B8 or B9)."

4-6) The authors have to explain exactly what the difference is between TARE and SIRT. What about combinational treatment of sorafenib + loco-regional therapies.

TARE means Trans Arterial Radio-Embolization, while the acronym SIRT means Selective Internal Radiation Therapy. The two acronyms are related to diverse devices but the therapy is the same. We think the results and the data about combination of loco-regional and systemic therapies have already been exhaustively exposed in the paragraph “Sorafenib treatment” (page 9 of the annotated copy).

4-7) Figure 2 and 3 are not really necessary to understand the review.

The reviewer is surely right, however, as we are radiologists, we prefer, if Editor agrees, to maintain the figures.

4-8) Figure 1: better keep potential second line therapies untitled. What is the meaning of other loco-regional therapies ?

The title named “Second line therapies” has been removed.
In the figure 1 we decided to discuss only the loco-regional therapies which have indication in advanced stage HCC: in particular we underline the possible role of TARE. The other loco-regional therapies (for example TACE or RFA) are not worldwide accepted in advanced stage disease treatment, so we preferred to omit them.

4-9) Table 1 Is lacking information about RFA.

As requested we have added in table 1 the following sentences about the indications and the results shown by RFA:
“Radiofrequency ablation is the second most commonly used technique (after TACE) to downstage HCC. In

selected patients with HCC ≤ 3 cm, this treatment shows similar results in terms of OS and disease recurrence than surgery[72]"

"According to BCLC algorithm radiofrequency ablation can be adopted essentially in two cases: in Child-Pugh A patients with single ≤ 2cm nodule (very early stage HCC) and in Child Pugh A-B patients(not eligible for liver transplantation) with 3 nodules smaller than ≤ 3 cm (early stage HCC) [72]"

4-10) Misspellings in the document have to be eliminated.

Done. The whole text has been revised