Author's response to reviews

Title: Clinical response to Auron Misheil therapy treatment in a patient with advanced multifocal hepatocellular carcinoma: a case report

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Author's response to reviews: see over
MS: 7561657784644387 - Clinical response to Auron Misheil therapy treatment in a patient with advanced multifocal hepatocellular carcinoma: a case report

Dear JMCR Editorial Team,

thank you very much for mailing the reviewer comments and for prolonging the resubmission deadline until the end of May.

Please find enclosed our manuscript, which we revised according to the reviewer's helpful suggestions and a detailed list with responses to the reviewer's comments. All amendments were highlighted in blue. Please note that we added Dr. Annette Dorn into the authors list.

Please let me know if there is any further information required.

I am looking forward to hearing from you.

Yours sincerely,

Prof. Dr. Dr. Jürgen Scheele
Response to Reviewer's Comments:

Reviewer 1 (Anna A Crocco):

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Reviewer 2 (Yongsong Guan):

1) The similarities between carcinogenesis and inflammation need explanation in the introduction or discussion section.

We inserted now a passage about the impact of inflammation on cancer induction and development into the introduction section.

2) There is no biopsy for histological result of the lesion's, so the authors should explain how to ensure that the lesions are HCC not other diseases such as focal nodular hyperplasia (FNH) and FNH-like lesions.

Biopsy of a liver nodule was performed in December 2003 and showed the typical histological features of an hepatocellular carcinoma. Thereafter typical radiological findings for a HCC in concordance with the AASLD guidelines were present over the whole time period. Therefore another biopsy was not performed.

3) Changes in AFP level during follow up should be provided.

AFP was measured 09/2008: 29,5 ng/ml, 10/2008: 27,5 ng/ml and 11/2008: 31,8 ng/ml. Thereafter, unfortunately no further measurements were performed.

Reviewer 3 (Liliana Montella):

1) The case report describes the effect of Auron Misheil therapy in a patient with advanced HCC. I think that the presumptive activity of this therapy should be better described in comparison with other therapeutic strategies, such as somatostatin and somatostatin analogues-based therapies. In particular, the Authors should briefly outline why insulin and somatostatin with apparent contrary effects could be active in HCC.
We inserted now a brief discussion about the mechanisms of AMT, somatostatin and structurally related substances in the conclusion section.

2) Dosages of AMT drugs and description of side-effects of treatment should be added to the paper.

We also inserted a description of an interim study into the "case presentation section", in which the adverse effects of AMT were analysed.

Reviewer 4 (Giuseppe Lombardi):

1) You write in "case presentation" section that patient started the treatment on September 11, 2008 but on January 30, 2009 the patient has a suspected adrenal involvement, thus the time to progression may be only 4 month. This value is lower than one obtained with standard sorafenib treatment (Llovet et al, NEJM, 2008) that was 5.5 months. So your treatment might be interesting if you can demonstrate by a biopsy or a MRI or a rational deduction that the lesion is not an adrenal metastasis to have a TTP 9 months.

Unfortunately we are not able to demonstrate that the adrenal involvement was not due to a HCC metastasis. However, Llovet et al. showed in their NEJM paper a median TTP of 24 weeks (5.5 months) for sorafenib. The 95% confidence interval was 18 weeks to 30 weeks, therefore our treatment is definitely in the same range (AMT in this patient TTP 20 weeks (4.7 months).

2) You write in "case presentation section" that ..."the patient refused sorafenib therapy". But why? Explain in more detail!

The patient refused therapy due to the well documented side effects (fatigue, diarrhoe, hand-foot-syndrome, etc.).

3) You write in "case presentation section" that .."the patient complained about dizziness during AMT and requested to terminate treatment". Is this the only side effect? Are there other side effects? Explain in more detail!
We inserted now the results of an interim study concerning possible other adverse effects of AMT treatment in this section.

4) In the "introduction section" the reference number 7 is not recent. Please insert a more recent review.


5) In the "introduction section" you write "HCCs are mostly resistant to chemotherapy". I suggest you mention the recent paper of Lombardi G, Zustovich F, et al (Cancer 2011) about the effectiveness of pegylated liposomal doxorubicin and gemcitabine in the treatment of HCC.

We inserted your publication into our manuscript.

6) In the "discussion section" might to speak about the possible role of this treatment in the patients with Child-Pugh B or C in which sorafenib treatment is not recommended.

Thanks for the comment; however, we think it would be too speculative to speak about the role of this treatment in patients with liver cirrhosis Child B or C.