

Format for ANSWERING REVIEWERS



January 10, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Disease Control with Sunitinib in Advanced Intrahepatic Cholangiocarcinoma Resistant to Gemcitabine-oxaliplatin Chemotherapy.

Author: Chantal Dreyer, Marie-Paule Sablin, Mohamed Bouattour, Cindy Neuzillet, Maxime Ronot, Safi Dokmak, Jacques Belghiti, Nathalie Guedj, Valérie Paradis, Eric Raymond, Sandrine Faivre

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13804

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

- (1) Ms. Title: Disease Control with Sunitinib in Advanced Intrahepatic Cholangiocarcinoma Resistant to Gemcitabine-oxaliplatin Chemotherapy. Authors: Chantal Dreyer and co-workers
The authors report their experience with three cases of sunitinib treatment for progressive cholangiocarcinoma. This tumor is difficult to treat and the observation of the authors could be of interest. The following points should be taken into consideration during possible revision: 1) Two/three patients were lost to follow-up. This limits the interpretability of the observations. Why was it impossible to get information on the further course. 2) Was none of the patients a candidate for liver transplantation? 3) The authors should state whether further patients with cholangiocarcinoma were treated with sunitinib at their institution. 4) The authors should cite the following article: Sweeney CJ, Chiorean EG, Verschraegen CF, Lee FC, Jones S, Royce M, Tye L, Liao KF, Bello A, Chao R, Burris HA. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. *J Clin Oncol.* 2010 Oct 10;28(29):4513-20.

Our revision: we thank the reviewer for his (her) important remarks that will improve the clarity of our report. Below are our answers point by point his (her) suggestions:

- 1) Two/three patients were lost to follow-up. This limits the interpretability of the observations. Why it was impossible to get information on the further course.

For 2 patients, the last available news were obtained when the patients left our unit to be managed for palliative care close to their home. Since their performance status deteriorated, no further anticancer treatment was provided: this was the reason why we did not get precise information on further course; particularly regarding the exact date of death.

We believe that this does not limit the interpretability of our observations for the following reasons:

-the patients had close follow-up during all the length of treatment with sunitinib;

-we secured all crucial information including safety, best response, date of progression under sunitinib, and lack of further anticancer treatment.

To comply with the reviewer's comment, details on patient outcome after sunitinib treatment were added in the manuscript:

Case#1. "Since the performance status of the patient further deteriorated, she was transferred to a palliative care unit in a primary center care close her home, the last news being available eight months after the second surgery."

Case#3. "The patient general condition further deteriorated, therefore she returned to her original country for palliative care management; the last news being available at the time of the end of sunitinib treatment."

2) Was none of the patients a candidate for liver transplantation?

None of those 3 cases was candidate for liver transplantation since the patients were either presenting a multifocal liver recurrence (case #1), extra-hepatic lymph node relapse (case#2), or locally advanced presentation at risk of extra-hepatic dissemination (case#3). Medical records of the 3 patients were discussed during multidisciplinary tumor board including liver surgeons experts in liver transplantation, medical oncologists, hepatologists, interventional radiologists, and pathologists. According to the center experience and published data, no indication for liver transplantation was proposed for these 3 patients because of the poor prognosis features for all 3 cases (tumor size, vascular invasion, progressive disease following chemotherapy).

3) The authors should state whether further patients with cholangiocarcinoma were treated with sunitinib at their institution: Those 3 patients were the first and only treated in our institution, their selection being made on the hypervascular pattern on CT scan. The interesting results observed in those 3 cases provided further rationale to design the SUN-CK proposal; therefore all other subsequent patients treated with sunitinib in our institution were included in the prospective phase II SUN-CK mentioned at the end of the manuscript (SUN-CK trial; NCT01718327).

4) The authors should cite the following article: Sweeney CJ, Chiorean EG, Verschraegen CF, Lee FC, Jones S, Royce M, Tye L, Liau KF, Bello A, Chao R, Burris HA. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. J Clin Oncol. 2010 Oct 10;28(29):4513-20: We thank the reviewer for proposing this reference. We inserted the proposed reference in the text of the discussion.

- (2) Reviewer 2: For Authors: While cholangiocarcinoma is the second-most common primary hepatic tumor after hepatocellular carcinoma (HCC), it is a rare disease, and the only curative treatment is surgical resection. Resectable cholangiocarcinoma is associated with frequent recurrence and a five-year survival rate of 20-40% following surgery, and when disease recurs, treatment with gemcitabine plus cisplatin is first-line therapy. However, there is currently no consensus on the best treatment option for patients presenting with disease progression following first-line therapy. The manuscript by Dreyer C. et al. described three cases of disease control with sunitinib in advanced intrahepatic cholangiocarcinoma resistant to gemcitabine-oxaliplatin chemotherapy. Angiogenesis and the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) play an important role in the pathogenesis of biliary tract cancers including cholangiocarcinoma, and therefore they applied sunitinib to treatment for recurrent cholangiocarcinoma resistant to gemcitabine-oxaliplatin chemotherapy. They showed promising results under therapy with sunitinib for recurrent intrahepatic cholangiocarcinoma. This paper is worth to be published in World Journal of Hepatology because it is innovative that sunitinib were used for recurrent cholangiocarcinoma resistant to gemcitabine-oxaliplatin chemotherapy in the clinical setting. The authors need to describe about the mechanism and side effect of sunitinib which they used in more detail for clinical use of this agent. Major compulsory revisions: 1. The authors need to describe about the mechanism and side effect of sunitinib which they used in more detail for clinical use of this agent

Our revision: The reviewer provides important remarks and we thank him (her) for the interest for our manuscript. We have considered his (her) suggestions as follows:

5) Major compulsory revisions: 1. The authors need to describe about the mechanism and side effect of sunitinib which they used in more detail for clinical use of this agent.

We have inserted more details about sunitinib side effects observed in the patients of the case report and provide an overview of the mechanism and side effects of sunitinib in the discussion section:

"Sunitinib is an oral multi-tyrosine kinases inhibitor targeting VEGFR, PDGFR, stem-cell factor receptor and fetal liver tyrosine kinase receptor 3. Sunitinib has shown potent antitumor and antiangiogenic activities with acceptable safety profile in patients with advanced solid tumors^[15-16]. Adverse events related to sunitinib are generally manageable, the most common side effects including asthenia, hand-foot syndrome, and hematological toxicities. Taken together, there is a strong rational to evaluate antiangiogenics, including sunitinib, in patients with intrahepatic forms of cholangiocarcinoma."

- (3) Third reviewer: This paper shows the employment of sunitinib in 3 patients with advanced intrahepatic cholangiocarcinoma progressive after standard chemotherapy. The results of this therapy in the advanced neoplastic disease are well demonstrated in each case reported. The discussion treats many points of view about the second-line chemotherapy and in particular the control of angiogenesis of tumor with the use of anti-angiogenic therapy. In conclusion the paper plays the role of precursor study for a prospective multicenter phase II trial with the sunitinib.

We are grateful to the reviewer's favorable comments and support on the importance for evaluating antiangiogenic therapy in patients with advanced cholangiocarcinoma based on the molecular rational.

3 References and typesetting were corrected

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

Sincerely yours,



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