

Format for ANSWERING REVIEWERS

February 29, 2016

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 24384-review.doc).

Title: Predictive effects of bilirubin on response of colorectal cancer to irinotecan-based chemotherapy

Author:

Qian-Qian Yu, Hong Qiu, Ming-Sheng Zhang, Guang-Yuan Hu, Bo Liu, Liu Huang, Xin Liao, Qian-Xia Li, Zhi-Huan Li, Xiang-Lin Yuan

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 24384

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

RESPONSES TO COMMENTS

General comment: The authors investigated the role of bilirubin level and UGT1A1*28 polymorphism in irinotecan based chemotherapy response evaluation. In the abstract the authors calculated the "CoBil" value which is combining the TBil and UBil. In conclusion they stated that "CoBil, as a routine testing index in clinic, after validation, could be easily used to facilitate stratification of mCRC patients for individualized treatment options". But in the result section they did not stratify the patients according to the CoBil value and did not define the "CoBil". TBil and UBil values were only taken into account. On the other hand the authors defined the CoBil at the Methods section. At the last sentences of results in the abstract the authors stating that "Classifier's performance of CoBil and UGT1A1*28 were comparable" but in the conclusion they only mentioned about the Cobil. This statement is confusing. Abstract should be rewritten briefly and more clear.

Reply: We completely agree and have rewritten the abstract accordingly. In the method section, we presented the cutoff values of TBil and UBil, and defined CoBil more clearly. In the result section, it was emphasized that patients were classified into three groups based on CoBil. In the conclusion section, both CoBil and UGT1A1*28 were included. The detailed modification was presented in the manuscript using track changes function.

At the results section under the subheading "4. Serum bilirubin levels and objective response", Sentences which is beginning with "Based on combined TBil and UBil values (CoBil)" can be given in a separate table in order to be more clear which defines the CoBil.

Reply: We completely agree and have demonstrated the CoBil data in a separate table.

- In the introduction "Irinotecan-based therapy is one of the most important fundamental

chemotherapy regimens for metastatic CRC (mCRC)." Sentences need references. Recently, in addition to irinotecan many drugs such as bevacizumab, regorafenib and ziv-aflibercept are recommended. After that sentences the authors pretty well described the pathophysiologic mechanism of irinotecan and study background.

Reply: We have added references after the sentence "Irinotecan-based therapy is one of the most important fundamental chemotherapy regimens for metastatic CRC (mCRC)".

- The selection of the patients and methods used are correct.

Thank you.

- At the "2. Clinical data collection" section "Cobil" used as "Cbil". Please use same abbreviations for consistency.

Reply: Sorry to make it confusing. "Cbil" is the abbreviation of "conjugated bilirubin". I have deleted the abbreviation for it was not mentioned in the other part.

- Using "Means and s.d.s" does not seem so good. Please prefer to using "means and SDs" in the text.

Reply: We completely agree and have modified the abbreviation accordingly.

-At the 3rd paragraph irintecan should be corrected.

Reply: Thanks for your patience and carefulness. We have corrected the word.

-In the conclusion the authors emphasized the predictive effect of the bilirubin levels but in the conclusion of abstract they stated the benefits of Cobil. They did not mention CoBil in conclusion.

Reply: We completely agree and have changed "baseline bilirubin levels" to "CoBil, as a parameter combining TBil and UBil values" in the conclusion.

- In discussion the authors described very brief results of previous studies and comment each of these investigations. Also compared their own results with other investigations. Finally they presented also limitations of their study. On the other hand, the discussion section should be more detailed.

Reply: We completely agree and have modified the text accordingly.

- In the last two sentences of discussion "in interventional clinical trials" should be replaced with "in international clinical trials"

Reply: We completely agree and have modified the text accordingly.

3 References and typesetting were corrected

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

Sincerely yours,

Xiang-Lin Yuan, PhD, MD, Professor of Medicine,

Department of Oncology, Tongji Hospital, Tongji Medical College,

Huazhong University of Science and Technology,

Wuhan, Hubei, 430030, P.R. China.

Telephone: +86-027-83663342

Fax: +86-027-83663342

Email: yxl@medmail.com.cn.