April 20, 2013
Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2895-review.doc).

Title: The efficacy of CapeOx regimen for extrahepatic metastasis of hepatocellular carcinoma following local treatments

Author: Shengli He; Jie Shen; Xianjuan Sun; Xiaojuan Zhu; Luming Liu; Jingcheng Dong

Name of Journal: *World Journal of Gastroenterology*
ESPS Manuscript NO: 2895
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) ***Reviewed by 01560071***

The authors investigated the safety of CapeOx regimen and its effects on survival after local treatments for HCC with extrahepatic metastasis. Because there would be few reports concerning this point, the presented data have some values. However, the median overall survival of 9.2 months are not sufficient, which may be obtained only by local treatments for intrahepatic HCC. At least, it is necessary to set a control group, in which only local treatments are performed without chemotherapy. In addition, there are many grammatical mistakes and misspellings, which should be corrected.

Response to the reviewer's comments: All patients who had undergone extrahepatic metastasis after local treatments were enrolled in this study. The primary objective of this study was to assess the overall response rate (21.9%), but the response rates were reported from 3% to 23% in several Phase II trials with targeted agents or in combination with chemotherapy in HCC, moreover, the TTP was reached 4.2 months. Phase Ⅱ clinical trial is exploratory, rather than confirmatory research, so more flexible design of the adaptive design, multi-stage and single arm trials can be used. In addition, many grammatical mistakes and misspellings had been corrected.

2. ***Reviewed by 00011221***

This study is an uncontrolled phase 2 evaluation of capecitabine and oxaliplatin for locally controlled HCC with extrahepatic metastases involving 32 patients, the majority of whom were HBV infected and non-cirrhotic. The majority of patients' metastases were pulmonary or intraabdominal with 6/32 being confined to bone. 28% of patients required dose reduction of capecitabine due to grade 3/4 toxicity but only 2 grade 3 oxaliplatin toxicities occurred. 31/32 patients died or manifested tumor progression. Median PFS was 4.2 mos and median OS was 9.2 months Criticism: 1. Was their an assessment of whether patients died from metastatic progression or intrahepatic recurrence/liver failure? 2. The authors should refrain from any language that implies superiority of capecitabine/oxaliplatin from sorafenib (which would be current standard of care). In this nonrandomized, uncontrolled phase II study, the authors can only claim safety and tolerability, but can make no claims regarding efficacy over non-treatment, superiority or inferiority over standard of care. OS 9.2 months is very similar to placebo arms for many similar trials, and in largely non-cirrhotic, treated HBV-infected patient group actually may be rather poor. This cannot be assessed without randomized, controlled phase IIb/III studies are completed.

Response to the reviewer's comments: Most patents died from metastatic progression (especially lung and peritoneal metastases), there were only five patients who died from liver failure induced by intrahepatic tumor recurrence, but there were no differences between metastatic progression and intrahepatic recurrence. We are very thankful you gave us so good advice about sorafenib is current standard of care for advanced HCC. This is only nonrandomized, uncontrolled phase II study. Based on this result, we will carry out a new randomized, controlled study (CapeOx vs Sorafenib) in several hospitals, we will stratify patients for trials (Cirrhotic and non-cirrhotic, HBV-infected and non-HBV infection, different PS and so on) between two groups.

3. ***Reviewed by 01560724***

This study aimed to investigate the efficacy and safety of a combination regimen of capecitabine plus oxaliplatin (CapeOx)

palliative chemotherapy for extrahepatic metastasis after local treatments of hepatocellular carcinoma. This is a well written study. Few minor comments: How many patients had Portal vein thrombosis? Variceal status of patients should be given. What were causes of death in patients who died? The lack of control group (placebo) makes claims of benefit sceptical. This should be addressed in discussion.

Response to the reviewer's comments: There were seven patients with portal vein tumor thrombosis, these tumor thrombosis are in segmental but not in main portal vein, so there was no serious variceal status which often leads to fatal complications. Most patents died from metastatic progression (especially lung and peritoneal metastases), there were only five patients who died from liver failure induced by intrahepatic tumor recurrence. This is only nonrandomized, uncontrolled phase II study. About the lack of control group (placebo) in this study, we had addressed in discussion.

4. ***Reviewed by 00053844***

Notes to authors: This is an interesting prospective study on efficacy of capecitabine and oxaliplatin (CapeOx) combination regimen for extrahepatic metastasis of hepatocellular carcinoma following local treatments, and gives a practical point of view in management of these patients. However, there are several clinical and methodological issues that should be addressed. When facing patients with neoplasm who have cirrhosis, clinicians may encounter some difficulties both in terms of choosing the appropriate treatment for cancer and of managing treatment-related hepatotoxicity and adverse liver events. It is important before starting cytotoxic chemotherapy to assess the aetiology and stage of liver disease and to screen these patients for portal hypertension and fluid retention. During cytotoxic chemotherapy, the effectiveness of cancer treatment, as well the appearance of early signs of hepatic decompensation, must be thoroughly monitored. These practical steps should be considered (Cabibbo G et al. Liver International 2011) Referee suggests to use Cox's proportional-hazard model to identify prognostic factors for mortality in a multiple regression analysis, and multiple logistic regression models to assess the relationship of both progression-free survival and adherence to therapy with the demographic, laboratory, clinical, and tumor staging characteristics of patients. From a clinical point of view, authors should provide data on liver function

deterioration, i.e. ascites development (due both to the treatment that the natural history of the disease). No data in the paper about the status of portal hypertension in cirrhotic patients. Physicians should, before beginning treatment, regularly monitor hepatic function and signs of portal hypertension (e.g., endoscopic evaluation for esophageal variceas) and appropriately treat. Finally, authors should be particularly concerned about the very small number of patients included in study. Due to the fact that sorafenib is not covered in the scope of health insurance for advanced HCC in China, although it is the standard systemic therapy for HCC, the authors should mention assessments of cost effectiveness of sorafenib in two countries: 1) NICE technology appraisal guidance 189 — Sorafenib for the treatment of advanced hepatocellular carcinoma www.nice.org.uk/guidance/TA189 2) Cammà C et al. Cost-Effectiveness of Sorafenib Treatment in Field Practice for Patients With Hepatocellular Carcinoma. Hepatology 2013.

Response to the reviewer's comments: Although there were seven patients with portal vein tumor thrombus, all tumor thrombus are in segmental but not in main portal vein. So patients had no several portal hypertension and fluid retention. Once patients with main portal tumor thrombus, we would consider tumor progression according to the Response Evaluation Criteria in Solid Tumors. Beginning and after treatment, we regularly monitored hepatic function (transaminases, alkaline phosphatases, bilirubin, lactate dehydrogenase, γ-glutamyltransferase, albumin, prothrombin time) and signs of portal hypertension. Treatment was continued until either disease progression; unacceptable toxicity.

We cited partial results from the two papers in discussion section （www.nice.org.uk/guidance/TA189 and Hepatology 2013. Although sorafenib is the standard systemic therapy for advanced HCC, there have not been widely used for these patients. In addition, we mentioned literature have reported some patients who did not benefit from sorafenib in our manuscript. Thank you very much for new information,we learned a lot .

5. ***Reviewed by 00051373***

It is a single arm study. Lack of a study controlled on the study design such as single agent (Capecitabine or Oxalipletin alon) and combined agents (Cape+ Oxa). 2. Case number is too small for analysis. 3. On the discussion section, almost all descriptions are come from the references. Lack of detail discuses the agents benefit for the advance hepatocellular carcinoma with metastatic lesions.

Response to the reviewer's comments: This is only nonrandomized, uncontrolled phase II study. Case number of patients was calculated according to a Simon optional two-stage design, assuming a response rate of 20%. With a power of 90%, this resulted in a sample size of nine patients for the stage. The size of second stage was determined by the observed number of responses and by the prespecified precision of 10%. There were three responders in the first stage. According to the study design, the sample size for the whole study was at least 30 patients.

6 ***Reviewed by 00070058***

The data presented shows a reasonable response rate associated with CapeOx in patients with extrahepatic metastases from HCC. In order to improve the manuscript, I would recommend: 1. Adding a table showing the multivariate analysis of potential prognostic factors on overall survival (even though none was statistically significant). 2. Editing for grammar, particularly in the discussion section.

Response to the reviewer's comments: Multivariate analysis of potential prognostic factors on overall survival had been done, OS was significantly longer in patients with a Child-Pugh class A compared with class B patients (as shown in Fig 2). We just described those results of no differences among others prognostic factors on OS in result section.

We have revised the grammatical mistakes and misspellings.

3 References and typesetting were corrected

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

Sincerely yours,

Shengli He

Department of Hepato-Biliary and Pancreatic Oncology, Fudan University Shanghai Cancer Center, Minhang Branch, Shanghai 200240, China.

E-mail: hlshli@yeah.net

Telephone: 0086- 021-64629290 Fax: 0086- 021-64633901