24 Feb, 2017

Prof. Ya-Juan Ma
Editor-in-Chief
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RE:Submission NO. 32585, "Phase I study of personalized peptide vaccination combined with radiotherapy for advanced hepatocellular carcinoma patients"

Dear Prof. Ya-Juan Ma,

Thank you for your last email with the reviewers' comments on our referenced manuscript. We have revised the manuscript in accordance with their comments, as follows:

Reviewer 1 Accept
Interesting study. I suggest to accept it in the current form.

Reviewer 2 Minor revision
The present study " Phase I study personalized peptide vaccination combined with radiotherapy for advanced hepatocellular carcinoma patients" includes a total of nine patients. Usually, the phase I study includes a small sample size (20 to 100, typically around 20). Despite the small number of patients included in the present study (nine patients with advanced hepatocellular carcinoma), it is interesting. The title reflects the contents of the manuscript. The structure is good and concise. However, the manuscript requires a number of corrections: "7 patients with multiple liver metastases (liver lesions >3 pieces), 1 patient with portal vein tumor thrombosis, 1 patient with bone metastasis, 3 patients with lung metastasis, and 1 patients with peritoneal metastasis" (Seven patients with multiple liver metastases…..)

Answer: Thank you very much for the advice and the efforts you have spent on this article. We totally have 9 patients in the study. According to table 1, we can find that some patients are with liver and lung or bone metastasis at the same time, and that's why we write as follows: *7 patients with multiple liver metastases (liver lesions >3 pieces), 1 patient with portal vein tumor thrombosis, 1 patient with bone metastasis, 3 patients with lung metastasis, and 1 patients with peritoneal metastasis*. **Now we have refined the sentences as follow since the description before is not correct enough:** A total of 9 patients with advanced hepatocellular carcinoma were admitted. Multidisciplinary consultation confirmed that all the patients were clearly no surgical opportunity. 4 patients with multiple liver metastases (liver lesions >3 pieces), 1 patient with liver metastases and

portal vein tumor thrombosis, 1 patient with lung and bone metastasis, 2 patients with liver and lung metastasis, and 1 patients with liver metastases and peritoneal metastasis.

Reviewer 3 Minor revision

In this paper, Jie Shen, et al. reported "Phase I study of personalized peptide vaccination combined with radiotherapy for advanced hepatocellular carcinoma patients".The issue proposed by the authors is an important and potential method in the future but some methodological shortcoming and the design should be clearly exposed.

Following some comments:

2. PATIENTS AND METHODS2.1 Patients" ------In which, 7 patients with multiple metastases?" This sentence was not clear.

2.2.1 RadiotherapyIn your team, what criteria decide patient accepting treatment strategies including dosage and duration?

3 Results1. This study presented therapeutic benefit for HCC patients; however, important laboratory data, for example bilirubin and albumin, need to be described because they could affect patient survival.

2. According to author, no significant adverse event was in this study. Why the patient 9 didn't continue treatment?

3. Different virus etiologies could induce different levels of immune response and clinical result; therefore, they need to be mentioned in the following study.Thanks!

Answer: Thank you very much for the advice and the efforts you have spent on this article. We try to answer the questions.

1) 2. PATIENTS AND METHODS2.1 Patients" ------In which, 7 patients with multiple metastases?" This sentence was not clear.

Now we have refined the sentences as follow since the description before is not correct enough:

A total of 9 patients with advanced hepatocellular carcinoma were admitted. Multidisciplinary consultation confirmed that all the patients were clearly no surgical opportunity. 4 patients with multiple liver metastases (liver lesions >3 pieces), 1 patient with liver metastases and portal vein tumor thrombosis, 1 patient with lung and bone metastasis, 2 patients with liver and lung metastasis, and 1 patients with liver metastases and peritoneal metastasis (Table1).

2) 2.2.1 RadiotherapyIn your team, what criteria decide patient accepting treatment strategies including dosage and duration?

In the discussion, we have explained why we choose this dose for radiotherapy. Generally speaking, radiotherapy may successfully immunize the patient against the cancer, converting the irradiated tissue into an in situ vaccine and endowing the host

with a set of new and powerful tools to master systemic disease. It is still unclear how the host-tumor relationship is affected by radiation, but it has been proved that when moving away from the 2Gy/fraction, 5-fractions-a-week conventional schedule to 5Gy/fraction-10Gy/fraction schedule, the immune effect will be more significant. Moreover, according to the clinical study of Prof. Zeng(The head of the radiology department of Shanghai Zhongshan Hospital), 5Gy/fraction schedule is an ideal dose for liver radiotherapy. Therefore, in this context, the radiotherapy dose we choose for liver and lung metastasis were 5Gy/fraction, 5-fractions-a-week schedule. For one thing, it can improve the local control, for the other thing, this schedule can increase immune effect. But we chose 4Gy/fraction, 5-fractions-a-week schedule for bone metastasis in order to protect the spinal cord. For peritoneal metastasis, we chose 0.5Gy/fraction BID, 2-fractions schedule with the purpose to deduce the side effect on colon and increase the effect of immune.

3) Results1. This study presented therapeutic benefit for HCC patients; however, important laboratory data, for example bilirubin and albumin, need to be described because they could affect patient survival.

The CHILDPUGH score of all those patients is A, except Patient3 with B. Therefore, the bilirubin of those patients is almost in the normal range, except Patient3 with a little bit higher, and the albumin of those patients is almost in the normal range, except Patient3 and 8 with a little bit lower. And the bilirubin and albumin did not change much after radiotherapy and immunotherapy. So we did not include this information.

4) 2. According to author, no significant adverse event was in this study. Why the patient 9 didn't continue treatment?

P3，P5 and P6 did not continue the therapy is because they live far away from our hospital, and it is not very convenient for them to receive the immune-based therapy. *P7 and P8* did not continue the therapy is because the treatment effect is not so ideal for them. P9 did not continue the therapy is because he has rash after therapy. P1, P2, P4 all continue the therapy and still follow-up now.

5) 3. Different virus etiologies could induce different levels of immune response and clinical result; therefore, they need to be mentioned in the following study.

All the patients here are HBV infected, but HBV DNA copy number is below 500IU/ml.