Reviewer's report

Title: Retrospective comparison between a regular and a split-dose protocol of 5-fluorouracil, cisplatin, and mitoxantrone for the treatment of far advanced hepatocellular carcinoma

Version: 1 Date: 12 December 2009

Reviewer: JASON CHIA-HSIEN Chia-Hsien CHENG

Reviewer's report:

This manuscript addressed the effects and the side effects of a split-dose of FMP chemotherapy regimen on grade III/IV neutropenia and overall survival in advanced hepatocellular carcinoma patients who had either main portal vein thrombosis and/or extrahepatic metastasis. In this article, patients who received chemotherapy (standard or split-dose of FMP) were still relatively favorable, indeed, around 30 to 50% HCC patients could not be enrolled into clinical trials of chemotherapy and might potentially not receive chemotherapy because of leucopenia or thrombocytopenia. Therefore, a split-dose of FMP regimen may be suggested in the use of treatment of highly selective HCC patients. However, the data and the generated conclusion might be seriously confounded by its retrospective nature and the patient selection bias, especially in the control group. Although it might be a potentially interesting paper, there are several points needing the clarification before it can be accepted for publication.

1. Chemotherapy still did some benefits in TAE-ineligible HCC patients. The FMP regimen (no matter standard or split course) really yield not so poor response in TAE-ineligible HCC patients, including extrahepatic metastases and portal vein thrombosis Sorafenib yielded in 9% RR in Child-Pugh A or B HCC patients (mainly Child A, not so many extrahepatic metastases and TAE-eligible). Combined target therapy will be the future trend but the cost is the major concern. On the other word, in selected patients, chemotherapy may still offer acceptable disease control but the toxicity should be paid with attention. Form this point, this article offer a possible choice of chemotherapy with acceptable disease control rate and toxicity profile. However, this article was not to compare and discuss the potential benefit and side effect of the chemotherapy regimens given in HCC patents; for example, anthracyclin-based chemotherapy regimen or etoposide-containing regimen. This issue should be discussed.

2. In multivariate analysis, HCV is a good prognostic marker for patients receiving chemotherapy. However, these findings are also found in thalidomide-treating patients. Therefore, this point should be discussed.

3. In “Result” section, the authors should assess and offer the hazard ratios of each individual character in multivariate analysis (Cox regression analysis). When these hazard ratios were demonstrated, the readers can clearly see the impact of these risk factors in HCC patients, for example, age, KPS, Child-Pugh
classification, extrahepatic metastasis, PV thrombosis, chemotherapy or not.

4. In “the age factor” of prognosis, the authors claimed that older age (elderly patient) is a good prognostic factor for patients who have been received chemotherapy. However, this finding did not seem reasonable and might be statistically controversial compared with other studies reported. It may be from the selection bias. This result should be cautiously presented, and it needs to be further validated.

5. In this article, the patient number in the control groups (who did not receive any chemotherapy regimen) was not comparable to patients who received chemotherapy. In your institute, we believe there may be more patients not receiving any chemotherapy because of the opinion of physicians, the findings of leucopenia and thrombocytopenia, etc. Therefore, the limited number and the selection bias in the control group may contribute to the worse survival. This information should be added, assessed, and discussed.

6. Among patients receiving a split-dose of FMP regimens, nearly 70% of patients received only one cycle of chemotherapy. Therefore, we though it is too early to claim the potential therapeutic value and limited toxicity profiles of the split-dose of FMPP regimen from the data. More comprehensive details of data of a split-dose of FMP in HCC patients should be offered to support your speculations. Especially in the current era; there are many choices of treatment strategies for HCC patients.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.