Dear Editor-in-Chief,

RE: Manuscript number 26283

I am submitting our revised manuscript on behalf of the authors by Law et al entitled "Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy". Please find below an explanation of how these comments have been addressed.

Reviewer 1

1. In page 4, line 14(Introduction), the authors use the term "reaction". I do suggest to replace it by the term "reactivation".

Response: The term "reaction" is replaced by "reactivation" in the introduction section.

2. Authors suggested algorithm for testing of HBV and management of patients with hematological malignancies receiving anticancer therapy in figure 1. However, this algorithm is personal opinion and table 3 describe the international guidelines on the management of patients with HBV infection receiving chemotherapy. I don't think figure 1 is necessary.

Response: We appreciate the point that the reviewer is making, but our experience indicates that algorithms and similar graphical elements enhance readers' ability to assimilate complex information. While recognizing that the content is personal opinion, it is based on sound medical evidence and clinical experience, and we hope that the reviewer can kindly consider allowing us to keep this algorithm.

Reviewer 2

3. Choice of antiviral therapies. In the last paragraph, authors stated that "Prophylaxis with telbivudine or adefovir is not recommended because of development of drug resistance and there are limited data from clinical trials using these agents" The reference was EASL guideline, yet, EASL guideline do not specify exact drug (telbivudine or adefovir). I agree that there are limited data with telbivudine or adefovir, yet, some reported good outcome with telbivudine (J Clin Virol 2014;61:199).

Response: The text of this section has been revised and the information from this citation included. The reference is also corrected and it should be AGA guideline instead of EASL guideline.

4. Duration of antiviral therapies. Authors may wish to add recent paper by Kim et al., where they reported importance of HBV DNA levels and consolidation period as a predictor of HBV reactivation after withdrawal of prophylactic antiviral therapy (Dig Dis Sci 2015;60:3794)

Response: The text of this section has been revised and the information from this citation included.

5. Management of HBV reactivation. Author stated that "Hepatitis B flare-ups are not rare in patients receiving cancer chemotherapy during and after anti-HBV prophylaxis, even when potent antivirals are used. If the patient is already receiving antiviral prophylaxis, switching to a more potent antiviral agent or combination regimens can be considered" The reference no 122 (J Med Virol. 2016 Mar 4. doi: 10.1002/jmv.24512. [Epub ahead of print]). Although the authors of ref. 122 concluded that "hepatitis B flare-ups are not rare in patients receiving cancer chemotherapy during and after anti-HBV prophylaxis, even when potent antivirals are used", when the reference was

reviewed, the HBV flare rate during antiviral prophylaxis was only 1.9% (six patients). I think the rate is quite low to say the reactivation rate is not"rare". Among these six patients, two patients were using entecavir. At diagnosis of HBV reactivation, these two patients did not show biochemical flare, and the duration of entecavir use was only one month for one patient. Therefore I think, evidence suggest hepatitis B flare-ups are rare when patients are receiving anti-HBV prophylaxis when potent antivirals are used. Furthermore, the next sentence may confuse the readers which are "switching to a more potent antiviral agent". If patients are using potent antivirals (e.g. entecavir or tenofovir), what is more potent antiviral agent ? The avoid any confusion, author should consider changing this statement. When patients are receiving lamivudine as a prophylaxis, they may develop resistance and may benefit from rescue therapy. The reference 122 study showed 3 cases, who has recovered after changing regimes to lamivudine + adefovir, entecaviro + adefovir, and tenofovir. It would be nicer to say "watch out for resistance when using low genetic barrier drug". Rescue regimen can be selected according to recent international guidelines for CHB.

Response: We have revised the content according to the reviewer's recommendation on hepatitis B flare-ups and rescued therapy. We agree that hepatitis B flare-ups are rare when patients are receiving anti-HBV prophylaxis when potent antivirals are used. When patients are receiving lamivudine as a prophylaxis, they may develop resistance and may benefit from rescue therapy. We need to watch out for resistance when using low genetic barrier drug.

6. Lastly, while reviewing ref. 122, I found that author list are correct. Please check references for the consistency and accuracy.

Response: We have checked the references for the consistency and accuracy.

We hope that, with these revisions, the article is now suitable for publication in your journal. I look forward to hearing from you soon.

Yours sincerely,

Man Fai Law