

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6875-Review.doc).

Title: Chemotherapy-related reactivation of hepatitis B infection: updates in 2013

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The manuscript has been improved according to the suggestions of reviewers. Comments from each reviewer and responses are as follows:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

I would like to congratulate the authors for this manuscript, which addresses a very important and current topic related to the management of HBV reactivation associated to chemotherapy. The manuscript is well structured and well written. The authors should discuss 1. Several risk factors have been published in the literature and have not been taken into account, such as male sex, young age, preexisting liver disease, lack of antiHBs antibodies. (Leo W, et al. J Clin Oncol 2009,, 27;605-11). Please consider to include a table on this matter 2. Chemotherapy related HBV reactivation in isolated anti-HBs positive patients (HbsAg negative and anti-HBc negative) (Ferreira R, Saudi J Gastroenterol 2012;18:277-81; Hui CK, Gastroenterology 2006;131:59-68).

Response: We thank the reviewer for this valuable comment. Indeed, we also cited Yeo et al.'s article (Ref. #17, J Clin Oncol 2009;27:605-11) in the Risk factors section of INTRODUCTION (page 6, lines 17-18). According to this comment, we added a sentence regarding additional risk factors at the end of the same paragraph (page 7, lines 6-17). And the case report of HBV reactivation in isolated anti-HBs-positive patient was added as a reference (Ref. #28). Taken together, known risk factors for HBV reactivation were summarized in Table 1.

Reviewer 2

This review is to address the current knowledge on the clinical aspects and management of chemotherapy-related HBV reactivation. The authors update the knowledge from recent reports and propose several unresolved issues and future perspectives. Minor revision 1. In this paper, "reactivation" should change to "HBV reactivation" in page 4 line 5, 13 and 17, page 5 line 18 and 23, page 6 line 16, page 7 line 23, and page 13 line 2. 2. References should be added in page 4 line 7 [...solid tumor (reference?)], page 7 line 3 [... (APASL) (reference 1, 31, 34)] and page 10 line 17 [.....recently (reference?)]. 3. A recent study (Hsu C, Tsou HH, Lin SJ, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study.

Hepatology. 2013, in press) can be discussed in the present manuscript.

Response: We are grateful to the reviewer for this comment. Accordingly, every “reactivation” was changed to “HBV reactivation”. The abovementioned references were added as recommended. Hsu et al.’s study (“accepted article” of Hepatology, 2013) was also covered in the revised manuscript (Ref. #39).

Reviewer 3

The issue is very important. The authors should review only some intriguing aspects of HBV reactivation following chemotherapy. I suggest to discuss the aspect regarding HBV reactivation in occult or past resolved infection. Only the following unresolved issues should be reviewed: 1) trials in occult infection 2) biologic drugs implicated in reactivation and the different risks (Please include a table). 3) Role of antiviral agents in pre-emptive prophylaxis 4) Role of HBV escape immunologic response and HBV escape mutants (reactivation may occur also despite prophylaxis with high genetic barrier drugs: see Rago A et al J Antimicrob Chemother. 2012 Feb;67(2):510-1.; Rago et al. Antivir Ther. 2010;15(6):929-32. 5) How to monitor patients for reactivation 6) When to stop prophylaxis and role of HBsAg quantification as predictor of HBV relapse I suggest to include in the ref. the following review by Mastroianni et al World J Gastroenterol. 2011 Sep 14;17(34):3881-7. Current trends in management of hepatitis B virus reactivation in the biologic therapy era.

Response: We thank the reviewer for all these important comments.

1) Trials in occult infection

A study by Huang et al. (J Clin Oncol 2013;31(22):2765-72) was cited in the manuscript (Ref. #51). Several studies on HBV reactivation in occult HBV infections were found on repeated literature research, and were added the Risk factors section of INTRODUCTION (page 7, lines 10-13).

2) biologic drugs implicated in reactivation and different risks

The main topic of this review article was anticancer chemotherapy-related HBV reactivation and its management. Biologic agents such as anti-TNF- α agents in inflammatory bowel diseases or rheumatoid arthritis are beyond the scope of this article. Therefore those agents were not covered this time.

3) Role of antiviral agents in pre-emptive prophylaxis

The role of ‘deferred preemptive’ strategy was covered in the Management section of INTRODUCTION (page 8, lines 8-12).

4) Role of HBV escape immunologic response and HBV escape mutants

We added mention on the possibility of immunological escape phenomenon from the cases in Journal of Antimicrobial Chemotherapy (2012;67(2):510-1) and Antiviral Therapy 2010;15(6):929-32 in LESSONS FROM RECENT REPORTS (page 14, lines 1-7).

5) How to monitor patients for reactivation

Monitoring of patients with occult/past HBV infection was mentioned in the Management section of INTRODUCTION (page 9, lines 20-22).

6) When to stop prophylaxis and role of HBsAg quantification as predictor of HBV relapse

- Treatment duration was described in the Management section of INTRODUCTION (page 8, lines

8-18).

- We also expect that HBsAg titer might be an important factor in HBV reactivation in terms of prediction of the clinical course or response to treatment. However, there is no sufficient data to support the use of HBsAg titer in prophylaxis of HBV reactivation during chemotherapy. We added some statements on this matter in UNRESOLVED ISSUES AND FUTURE PERSPECTIVES (page 17, lines 11-14).

Reviewer 4

The goal of this review is to outline the clinical and management aspects of chemotherapy related HBV reactivation. The authors clearly outline the definition of inactive carrier and reactivation. 1. The risk factors are well defined although it would be interesting to lay out which HBV mutations are at a higher risk for reactivation. 2. The discussion on HBV core antibody positive patients at the end of the Risk Factor section is confusion. I recommend simplifying the sentences to make them concise and clear. 3. Management section is informative and well written 4. Recent literature is well reviewed and the tables are informative. 5. Areas of uncertainty are explained and presented well. Overall well written and informative review.

Response: We thank the reviewer for these thoughtful comments. Specific mutants with higher risk for HBV reactivation were added in the Risk factors section of INTRODUCTION (page 7, lines 1-3). The last part of the Risk Factor section was more clearly rewritten (page 7, lines 6-17).

3 References and typesetting were corrected

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

Sincerely yours,

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