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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86024

Title: Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies in the targeted therapy era

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00052947
Position: Peer Reviewer
Academic degree: MD
Professional title: Director, Professor
Reviewer's Country/Territory: Germany
Author's Country/Territory: China

Manuscript submission date: 2023-05-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-31 16:11

Reviewer performed review: 2023-06-11 16:31

Review time: 11 Days

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

General comment The topic of the review is highly relevant and timely. The merit of the review is that it covers the entire spectrum of drugs or therapies against hematologic malignancies. Overall, the text is well organized. The tables are informative, but the layout is partly suboptimal. A weakness is the virtual absent description of the HBV replication and the effect of anti-HBV immune reactions on the course of the infection. A small paragraph on the life cycle with its persistent nuclear cccDNA and the role of immune pathogenesis in acute and chronic hepatitis B. The sensitivity and specificity of the HBV screening tests is not even touched. A further weakness is the inaccurate distinction between HBV infection and HBV induced disease. The nomenclature should be clearer and more consistent. Specific points 1. Title. Spell out HBV in the title 2. The abstract and core tip should more clearly and explicitly mention that inactive and even "resolved" HBV infection leads virtually always to persistence of HBV genomes in the liver. The expression of those silent genomes is controlled by the immune system. Suppression or ablation of immune cells, most importantly B cells may lead to reactivation of seemingly resolved HBV infection. 3. Introduction, 1st sentence. "Patients

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with chronic or resolved hepatitis B virus (HBV) infection are at risk of reactivation of the virus if they receive chemotherapy or immunotherapy. " The nomenclature should be more precise. a. Not all chemotherapies are immunosuppressive. b. Immunotherapy could be used to actively suppress HBV or cancer cells. 4. Virologic factors. "The identified virologic risk factors for include CHB, high baseline HBV DNA levels and hepatitis B e-antigen (HBeAg) positivity". Again, the wording is unfortunate: a. Risk factor for what? Reactivation or CHB? b. An HBV infection with high HBV DNA and with HBeAg is already very active and cannot be reactivated anymore. However, reactivation of the inactive immune response will lead to an acute flare or even liver failure. 5. The work of Salpini et al (ref. 21) is incorrectly described. There, it is indeed mentioned that 5 mutations were in T cell epitopes but most of the mutations were in the B cell epitopes of the HBs antigenic loop. This is in line with the frequent reactivation under B cell suppressive therapy. 6. "Obinutuzumab is a second-generation anti-CD20 monoclonal antibody. It is a humanized, glycol-engineered type 2 antibody". There is an embarrassing mistake: It has nothing to do with glycol. It has non-fucosylated sugars on the Fc portion. 7. HBV screening. The text should cover rare cases as well. Fig. 1 is indeed helpful. a. HBsAg may be false negative due to diagnostic escape mutations. b. Anti-HBc may be false negative after a previous B cell depleting therapy. (Gärtner et al. Permanent loss of anti-HBc after reactivation of hepatitis B virus infection in an anti-HBs and anti-HBc-positive patient after allogeneic stem cell transplantation. J Clin Virol. 2007 PMID: 17182277. c. Isolated anti-HBs without anti-HBc may be present in pretreated patients without previous HB vaccination. d. For all three cases a sensitive test for HBV DNA is advisable. 8. HBsAg-positive patients without hepatitis at baseline. The problem here is that the immunosuppressive therapy may initially increase the viral load without ALT rise. However, if immune reconstitution occurs, a fulminant hepatitis may result which cannot be treated with NAT anymore. The same can occur with HBsAg negative

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patients. 9. CHOICE OF ANTIVIRAL THERAPY. It should be mentioned that previous lamivudine therapy often leads to selection of mutants which may become rapidly resistant to entecavir. Geipel A et al. Entecavir allows an unexpectedly high residual replication of HBV mutants resistant to lamivudine. Antivir Ther. 2015;20(8):779-87. PMID: 25560463. 10. Tables 1-5 report the number of deaths caused by reactivation as zero throughout. However, many historical case reports exist with a lethal course of HBV reactivation under immunosuppressive therapy, e.g.: Foont JA, Schiff ER. Avoid the tragedy of hepatitis B reactivation in immunosuppressed patients. Nat Clin Pract Gastroenterol Hepatol. 2007 PMID: 17262070.

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Position: Peer Reviewer
Academic degree: N/A
Professional title: N/A
Reviewer's Country/Territory: Poland
Author's Country/Territory: China

Manuscript submission date: 2023-05-29

Reviewer chosen by: AI Technique

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Review time: 1 Hour

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No orgiginal findings of this manuscript