REPLY TO THE COMMENTS

* REPLY TO REVIEWER 1

Comment 1. I am aware that the paper is to be used as a practical guide for clinicians; however, it is unclear what the screening is for (e.g., antibodies, viral proteins, antigen, RNA levels, Etc.). Additionally, it is poorly described which diagnostic techniques the authors refer to for HCV screening and their respective advantages and disadvantages.

Reply to comment 1: Anti-HCV antibody is a recommended tool for initial screening of HCV infection in cancer patients receiving chemotherapy because of its cheap and cost-effective advantages. However, the disadvantage of screening HCV infection by serum anti-HCV antibody is a positive result indicating either current or past HCV infection. Therefore, cancer patients with a positive result of anti-HCV antibody should be further tested for serum HCV RNA to confirm current infection status of HCV (Please see **Figure 1**). In clinical practice, serum HCV RNA is not recommended as a routine screening tool for HCV infection in cancer patients because it is an expensive diagnostic method. We have demonstrated the algorithm for testing and treating hepatitis C virus infection in cancer patients receiving chemotherapy in **Figure 1**. Additionally, we also discuss the advantages and disadvantages of anti-HCV antibody and HCV RNA in the screening of HCV infection in cancer patients undergo chemotherapy (P8, line 15: *Anti-HCV antibody is a recommended tool for initial screening of HCV infection in cancer patients receiving chemotherapy because of its cheap and cost-effective advantages. However, the disadvantage of screening HCV infection by serum anti-HCV antibody is a positive result indicating either current or past HCV infection. Therefore, cancer patients with a positive result of anti-HCV antibody should be further tested for serum HCV RNA to confirm current infection status of HCV. In clinical practice, serum HCV RNA is not recommended as a routine screening tool for HCV infection in cancer patients because it is an expensive diagnostic method.*).

Comment 2. Table 1 is, in my view, not necessary.

Reply to comment 2: According to the reviewer's valuable comments, we have deleted Table 1, and described the contents in the Table 1 of original manuscript in the text of revised manuscript (P5, line 12: *In a retrospective observation study by Lee et al. [16], enhanced replication of HCV (increase in HCV-RNA level of ≧ 1 log_{10} IU/mL over baseline) was noted in 9 (27%) of 33 HCV-infected cancer patients who underwent chemotherapy. Another retrospective study by Talima et al. [17]*

demonstrated that the incidence of HCV reactivation (increase in HCV-RNA level of ≧ 1 log_{10} IU/mL over baseline) in 34 HCV-infected breast cancer patients receiving chemotherapy was 6% (2/34). In a prospective observation study by Torres et al. [18], reactivation of HCV infection (increase in HCV-RNA level of ≧ 1 log_{10} IU/mL over baseline) occurred in 23 (23%) of 100 cancer patients undergoing chemotherapy. Among these cancer patients, those with hematological malignancies had a higher incidence of HCV reactivation than those with solid tumors (36% vs. 10%).).

Comment 3. Since the manuscript is poorly illustrated, information in tables 2 and 4 could be transformed in Figures.

Reply to comment 3: According to the reviewer's constructive comments, we transformed Table 4 in the original manuscript to a figure (**Figure 1** in the revised manuscript; P18: ***Figure 1.*** *Current recommendations for testing and treating hepatitis C virus infection in patients receiving chemotherapy*.). Because the contents of Table 2 in the original manuscript are very complex, it is difficult for us to illustrate them with a figure. We therefore have not transformed it to a figure. We are very sorry for that and thank the reviewer's valuable comments.

Comment 4. Font size and formatting of table 4 are not the same as the other tables.

Reply to comment 4: Because Table 4 in the original manuscript is transformed to a figure according to the reviewer's comments, it is no longer present in the revised manuscript.

We sincerely thank the reviewer's valuable and constructive comments!

*** REPLY TO REVIEWER 2**

Comment 1. What is the definition of HCV reactivation? - It is not clearly defined. - Moreover more than one meaning was mentioned within the manuscript. - It should be clearly defined before discussing the topic What is the definition of quiescent HCV infection? - Is it an HCV infection with positive HCV-RNA but normal liver enzymes? or - Is it an HCV infection with positive HCV-RNA but normal liver biopsy or those with minimal activity and no fibrosis? Or what? A highlight should be given on the different definitions of HCV-related hepatitis flare in cancer patients before discussing this title.

Reply to comment 1: According to the reviewer's valuable comments, we summarize the definitions of quiescent HCV infection, HCV reactivation and HCV-related hepatitis flare recommended by authors in **Table 1** in the revised manuscript. The definition of quiescent HCV infection is an HCV infection with a positive serum HCV-RNA and normal serum levels of liver enzymes. The recommended HCV reactivation during chemotherapy is increase in HCV-RNA level of ≧ 1 $\log_{10}$ IU/mL over baseline. The recommended definition of HCV-related hepatitis flare is unexplained increase in ALT to 3 times the upper limit of normal during chemotherapy and increase in HCV-RNA level of ≧1 $\log_{10}$ IU/mL over baseline. Additionally, we list the definitions of HCV-related hepatitis flare in each study quoted in the **Table 2**. The importance of the definitions of HCV reactivation and HCV-related hepatitis flare during chemotherapy is also addressed in the text (P 4, line 4 from below: *This article summarizes current evidences dealing with HCV reactivation and HCV-related hepatitis flare in cancer patients receiving chemotherapy. It is worthy to note that the definitions of HCV reactivation and hepatitis flare during chemotherapy varied in previous studies [4,17-22]. In this review article, we list the definitions of HCV reactivation and HCV-related hepatitis flare in each study quoted in the Tables. The definitions of HCV reactivation and HCV-related hepatitis flare recommended by authors are summarized in* ***Table 1****. Recommended HCV reactivation during chemotherapy is increase in HCV-RNA level of ≧ 1 $\log_{10}$ IU/mL over baseline [17], and recommended definition of HCV-related hepatitis flare is unexplained increase in ALT to 3 times the upper limit of normal during chemotherapy and increase in HCV-RNA level of ≧1 $\log_{10}$ IU/mL over baseline [18]. Most retrospective works lacked the data of HCV viral load before chemotherapy. The scientific strengths of these retrospective evidences were therefore not robust.*).

Comment 2. Page 7: What is the evidence-base for the need of chemotherapy stoppage in those with HCV-reactivation?

Reply to comment 2: Based on the elevation of liver transaminases, bilirubin, alkaline phoaphatase, and clinical features of liver insufficiency, the World Health Organization has developed liver toxicity criteria classifying hepatic damage into five grades (0-4). Depending on the grade, a decision should be made as to whether dose modifications or discontinuation of chemotherapy is required (Semin Oncol 2005.11.002). Currently, there are no randomized controlled trials comparing the outcomes of the patients with chemotherapy-related HCV reactivation who stop chemotherapy and who go on cancer treatment. Therefore, whether chemotherapy should be stopped in cancer patients with HCV reactivation remains unclear. However, physicians often discontinue chemotherapy in HCV-infected cancer patients who develop severe liver dysfunction during cancer treatment because it is a life-threatening condition and can be induced by chemotherapeutic drugs or HCV reactivation. We have addressed this issue in the revised manuscript (P6, line 7: *Currently, there are no randomized controlled trials comparing the outcomes of the patients with chemotherapy-related HCV reactivation who stop chemotherapy and who go on cancer treatment. Therefore, whether chemotherapy should be stopped in cancer patients with HCV reactivation remains unclear. However, physicians often discontinue chemotherapy in HCV-infected cancer patients who develop severe liver dysfunction during cancer treatment because it is a life-threatening condition and can be induced by either chemotherapeutic drugs or viral reactivation.*).

Comment 3. MD Anderson----- please write MD Anderson Cancer Center.

Reply to comment 3: We will correct "MD Anderson" to "MD Anderson Cancer Center".

We sincerely thank the reviewer's valuable and constructive comments!