ORIGINAL ARTICLE

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Reactivation of Hepatitis C Virus and Its Clinical Outcomes in Patients Treated with Systemic Chemotherapy or Immunosuppressive Therapy

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Background/Aims: According to the results of several studies, the outcome of hepatitis C virus (HCV) reactivation is not as severe as the outcome of hepatitis B virus reactivation. The aim of this study was to evaluate the effect of pharmacological immunosuppression on HCV reactivation. **Methods:** The medical records of patients who underwent systemic chemotherapy, corticosteroid therapy, or other immunosuppressive therapies between January 2008 and March 2015 were reviewed. Subsequently, 202 patients who were seropositive for the anti-HCV antibody were enrolled. Exclusion criteria were: unavailability of data on HCV RNA levels, a history of treatment for chronic hepatitis C, and the presence of liver diseases other than a chronic HCV infection. **Results:** Among the 120 patients enrolled in this study, hepatitis was present in 46 patients (38%). None of the patients were diagnosed with severe hepatitis. Enhanced replication of HCV was noted in nine (27%) of the 33 patients who had data available on both basal and follow-up HCV RNA loads. Reappearance of the HCV RNA from an undetectable state did not occur after treatment. The cumulative rate of enhanced HCV replication was 23% at 1 year and 30% at 2 years. **Conclusions:** Although enhanced HCV replication is relatively common in HCV-infected patients treated with chemotherapy or immunosuppressive therapy, it does not lead to serious sequelae. **(Gut Liver 2017;11:870-877)**

Key Words: Hepatitis; Hepacivirus; Immunosuppression; Viral replication

INTRODUCTION

The worldwide prevalence of hepatitis C virus (HCV) infection is 1.6%, or about 115 million people. Exposure to HCV tends to result in chronic persistent infection in 50% to 80% of immunocompetent hosts, which if untreated can lead to advanced liver disease, such as liver cirrhosis (LC) and hepatocellular carcinoma.[1] As not only HCV but also hepatitis B virus (HBV) are noncytopathic, the host immune system has a crucial role in inducing liver disease, including immune-mediated disease pathogenesis or viral clearance.[1]

HBV reactivation has been reported to cause fatal outcomes in some patients. Risk factors for HBV reactivation include use of rituximab or corticosteroids, breast cancer, transarterial chemoembolization, and undergoing hematopoietic stem cell transplantation (HSCT).[2-5] Guidelines have been established for preemptive antiviral therapy in HBV-infected patients undergoing chemotherapy or immunosuppressive therapy. The pathogenesis of hepatitis virus reactivation is not fully understood, though it is generally divided into three stages. Following induction of immune suppression, viral reactivation starts with an increase in replication. After treatment discontinuation, the immune system recovers and attacks infected hepatocytes. Ultimately, hepatitis resolves, and viral replication returns to baseline levels during the recovery stage.[3] This pathogenic mechanism of viral reactivation is thought to be similar in HBV and HCV. However, HCV reactivation usually follows a mild clinical course, and cases of severe hepatitis or hepatic decompensation are rare in contrast to HBV infection.[6-8]

To date, no guidelines for the management of HCV reactiva-

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tion have been established due to a lack of evidence from previous studies, which complicates the decision to treat when viral titers begin to increase. Therefore, we aimed to investigate the effect of pharmacological immunosuppression–such as systemic chemotherapy, corticosteroids or other immunosuppressive therapy–on HCV patients, focusing on viral reactivation, hepatitis and hepatic decompensation.

MATERIALS AND METHODS

1. Patients

We screened patients who received systemic chemotherapy, corticosteroids or other immunosuppressive therapy in the hematology, oncology or rheumatology department and monitored anti-HCV antibody status between January 1, 2008 and March 1, 2015 at a tertiary medical center in South Korea. Among them, 202 patients seropositive for anti-HCV antibody were enrolled in the study. Patients were excluded from the study for the following reasons (n=82): unavailable information on HCV RNA levels (n=28), history of treatment for chronic hepatitis C (n=18) and other liver diseases (n=36), such as chronic hepatitis B, autoimmune hepatitis, alcoholic liver disease and hepatocellular carcinoma. All patients had available results for anti-HCV antibodies, white blood cell counts with differential count, platelet counts, prothrombin time, alanine aminotransferase (ALT), albumin and total bilirubin at baseline before starting treatment for their underlying diseases. Seropositivity for anti-HCV antibody was determined using third-generation enzyme immunoassays (Abbott Laboratories, North Chicago, IL, USA). The HCV RNA level was determined by real-time polymerase chain reaction (Biosewoom Inc., Seoul, Korea). To evaluate HCV RNA reactivation, we collected data from all patients with available HCV RNA levels before and after starting treatment, irrespective of the frequency and interval. This study was approved by the Institutional Review Board/Ethics Committee of Seoul St Mary's Hospital of the Catholic University of Korea (KC16RISI0331). Because of the retrospective nature of this study, informed consent was not required.

2. Definitions

Hepatitis was defined as a 3-fold increase in the ALT level over baseline or >100 U/L (reference range, <36 U/L) that developed during treatment or up to 3 months after the last treatment in the absence of other hepatotoxic drugs except treatments for underlying diseases. Cases of drug-induced hepatitis due to systemic chemotherapy, corticosteroids or other immunosuppressive therapies were included because it was difficult to differentiate them from hepatitis caused by enhanced HCV replication. Cases of hepatitis caused by tumor invasion of the liver or systemic infections were excluded.[3,6] Severe hepatitis was defined as an increase of ALT to >10-fold the upper limit of normal (ULN). Hepatic decompensation was defined by the occurrence of any of the following: newly developed encephalopathy or ascites, increase in the prothrombin time of >3 seconds relative to the baseline, or increase in the bilirubin level to twice the ULN (reference range, <1.2 mg/dL) or twice the baseline level if initially abnormal.[9] Enhanced HCV replication was defined as the reappearance of RNA previously undetected or increased by >1 $\log_{10}$ IU/mL compared with baseline, as defined in previous studies.[3,4,6,10] LC was defined by the presence of cirrhotic changes, such as liver parenchymal coarseness or a nodular surface on liver imaging, and/or there was clinical evidence of portal hypertension (e.g., ascites, gastroesophageal varices, or splenomegaly with a platelet count <100,000/mm^3).

3. Statistical analysis

Analyses were conducted using an independent sample t-test, Mann-Whitney U-test, chi-square test and Fisher exact test, as appropriate. Two-tailed p-values of <0.05 were considered to indicate significance. Logistic regression was used to identify risk factors for enhanced HCV replication. Variables determined to be significant in univariate analyses were included in a multivariate analysis. Data were analyzed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

1. Study population

The baseline characteristics of the 120 patients are shown in Table 1. Underlying diseases of patients who received chemotherapy or immunosuppressive therapy were divided into the following three categories: solid tumors (n=42, 35%), hematological tumors (n=40, 33%) and other diseases (n=38, 32%), which included kidney transplantation (n=10), rheumatoid arthritis (n=6), inflammatory bowel disease (n=2) and other medical problems (n=20). The most frequently used treatment regimens are described in Table 1. Among the 120 patients, 13 underwent HSCT and 10 received rituximab-containing regimens. Most patients had well-maintained baseline liver function, but 10 (8%) were diagnosed with LC before starting treatment. The Child-Turcotte-Pugh class of LC was A in eight patients and B in two patients, who had a score of 7 due to an albumin level of <2.8 g/dL. The anti-hepatitis B core antibody status was evaluated in 56 patients because this parameter was not routinely checked at departments other than gastroenterology; 37 (66%) of these patients were positive, indicative of a history of HBV infection. Of the patients, 85 (71%) had a normal ALT level (<36 IU/L), and the median HCV RNA level was 84,200 IU/mL. Information on the HCV genotype was available in 56 patients (47%), among whom genotypes 1b and 2 were the most common, as in the general Korean population (31 [55%] and 24 [43%] patients, respectively); one patient (2%) had genotype 3. The median follow-up duration was 29.2 months (range, 0.4–98.9 months).

Table 1. Baseline Characteristics of Patients Positive for the Anti-HCV Antibody Who Received Systemic Chemotherapy or Immunosuppressive Therapy (n=120)

Characteristic	Value
Age, yr	54±14
Male sex	57 (48)
Disease category	
Solid tumor	42 (35)
Hematological tumor	40 (33)
Others*	38 (32)
Treatment	
Hematopoietic stem cell transplantation	13 (11)
Rituximab-containing regimen	10 (8)
Immunosuppressive agents†±corticosteroids	15 (13)
Corticosteroids only	23 (19)
Other‡	59 (49)
Baseline laboratory findings	
WBC, /μL	6,942±7,684
Platelets, 10^9/L	187±102
Prothrombin time, INR	1.08±0.12
Albumin, g/dL	4.1±3.3
ALT, U/L	30±24
ALT <36 U/L	85 (71)
Total bilirubin, mg/dL	0.68±0.35
Liver cirrhosis	10 (8)
Anti-HBc IgG	
Negative	19 (34)
Positive	37 (66)
HCV RNA, IU/mL	84,200 (not detected–2.9×10^6)
HCV genotype (1a/1b/2/3)	0/31 (55)/24 (43)/1 (2)

Data are presented as mean±SD, number (%), or median (interquartile range).
HCV, hepatitis C virus; WBC, white blood cell; INR, international normalized ratio; ALT, alanine aminotransferase; HBc, anti-hepatitis B core antibody.
*Kidney transplant recipients (n=10), rheumatoid arthritis (n=6), inflammatory bowel disease (n=2), and other medical problems requiring treatment with immunosuppressive agents with or without corticosteroids (n=20); †Azathioprine, methotrexate, cyclosporine, tacrolimus, and so forth; ‡Various chemotherapeutic agents were used to treat solid and hematological tumors.

2. Hepatitis in HCV patients who underwent chemotherapy or immunosuppressive therapy

The patients were divided into two groups according to the presence of hepatitis (Table 2). Of the 120 patients, 46 (38%) had hepatitis during and after treatment. There was no significant difference in baseline laboratory findings between the two groups. Of the patients with detectable HCV RNA levels (n=72), 31 patients (44%) had hepatitis and 41 (56%) did not. Although there was a difference in the incidence of hepatitis when patients were grouped according to disease category (it was significantly high in patients with a solid tumor while low in patients with other diseases), there was no significant difference when the patients were grouped according to treatment modality except that hepatitis was rarely noted in patients treated with only corticosteroids (1/19, 5%). The prevalence of LC was comparable between the two groups; 13% (n=4) versus 15% (n=6) in patients with and without hepatitis, repectively. The treatments for underlying diseases were delayed in 10 of 31 patients (32%) with hepatitis and three of those patients died during the admission period when hepatitis occurred. The causes of death were disease progression (n=2) and systemic infection (n=1), and HCV RNA levels were not recorded at that time. There were no cases of severe hepatitis or hepatic decompensation.

3. Enhanced HCV replication in patients who underwent chemotherapy or immunosuppressive therapy

Information on the HCV RNA levels before and after treatment was available for 33 patients. Enhanced HCV replication was detected in nine patients (27%), and HCV RNA levels fluctuated in the other patients. Only the proportion of patients with LC was a significant factor in the univariate analysis (Table 3), and it was significantly higher among those with enhanced HCV replication (hazard ratio, 18.4; 95% confidence interval, 1.78 to 201.9; p=0.004). Data on HBV markers were available on follow up for 23 patients and there was no case of HBV reactivation represented by a positive result for HBsAg or detectable HBV DNA that had been negative. There was no case of reappearance of HCV RNA from a negative to a detectable state after treatment. The median follow-up duration in the 33 patients was 27.2 months (interquartile range, 9.6 to 50.7 months). The cumulative rate of enhanced replication of HCV was 23% at 1 year and 30% at 2 years.

4. Clinical features of patients with enhanced HCV replication

Because of the heterogeneity of underlying diseases and treatments, the clinical courses of patients with enhanced HCV replication were diverse (Table 4). Six of nine patients (67%) showed hepatitis associated with enhanced HCV replication and in one of them, systemic chemotherapy was discontinued due to worsened clinical condition, not hepatitis. Six patients were alive at the last follow-up; two patients died due to disease progression and one was lost to follow-up. The increase in HCV RNA levels was greater in patients with hematological tumors than in those with other diseases. The HCV RNA level in the patient diagnosed with hemophagocytic lymphohistiocytosis was 6×10^3-fold higher than at baseline, and the ALT level was 3-fold higher than the baseline value but did not exceed 100 IU/L. The patient diagnosed with diffuse large B-cell lymphoma (DLBCL) showed a considerable increase in HCV RNA levels and had the highest posttreatment ALT levels among the nine patients. However, this did not delay subsequent treatment for DLBCL.

Table 2. Comparison of HCV-Infected Patients with and without Hepatitis Who Had Detectable HCV RNA Levels

	Patients with hepatitis	Patients without hepatitis	p-value*
No. of patients	31 (44)	41 (56)	
Age, yr	53±14	58±12	0.17
Male sex	12 (39)	17 (41)	0.568
Disease category			0.001*
Solid tumor	14 (45)	8 (20)	0.02*
Hematological tumor	11 (35)	7 (17)	0.07
Others†	6 (19)	26 (63)	<0.001*
Treatment			0.001*
Hematopoietic stem cell transplantation	2	1	0.40
Autologous/allogenic	0/2	1/0	
Rituximab-containing regimen	3	1	0.18
Immunosuppressive agents‡±corticosteroids	3	7	0.37
Corticosteroids only	1	18	<0.001*
Others§	22	14	0.004*
Baseline laboratory findings			
WBC, /μL	4,860±2,295	6,915±8,314	0.47
Platelets, 10^9/L	183±133	195±104	0.75
Prothrombin time, INR	1.0±0.0	1.01±0.12	0.72
Albumin, g/dL	3.7±0.5	3.8±0.6	0.44
ALT, U/L	35±22	34±28	0.92
Total bilirubin, mg/dL	0.67±0.5	0.72±0.48	0.75
Liver cirrhosis	4 (13)	6 (15)	0.83

Data are presented as number (%) or mean±SD.
HCV, hepatitis C virus; WBC, white blood cell; INR, international normalized ratio; ALT, alanine aminotransferase.
*Means, median or numbers significantly different between the two groups, p-value <0.05; †Kidney transplant recipients (n=10), rheumatoid arthritis (n=6), inflammatory bowel disease (n=2), and other medical problems requiring treatment with immunosuppressive agents with or without corticosteroids (n=20); ‡Azathioprine, methotrexate, cyclosporine, tacrolimus, and so forth; §The rest of the other treatments including various systemic chemotherapies.

DISCUSSION

The prevalence of HCV reactivation is lower than that of HBV reactivation in patients undergoing chemotherapy or immunosuppressive therapy, and the clinical outcome is not severe.[3,4,6,11,12] However, due to a lack of studies on HCV reactivation, appropriate interventions against the underlying disease or HCV infection may not be done. Indeed, data on the risk factors, prevalence and clinical outcomes of HCV reactivation are insufficient. Our findings indicated enhanced HCV replication in 27% of patients; however, this did not lead to serious sequelae.

In this study, hepatitis was noted in 38% of all patients and in 44% of those with detectable HCV RNA levels, as well as in 31% of patients in whom anti-HCV antibody was positive and HCV RNA negative. Although HCV-infected patients had a high prevalence of hepatitis, there was no significant difference among these groups (p=0.384). Some previous studies have suggested that the incidence of hepatitis in HCV-infected patients under pharmacological immunosuppression does not differ from that of non-HCV-infected patients,[7,13] but in other studies the incidence of hepatitis following chemotherapy or immunosuppressive therapy differed between HCV- and non-HCV-infected patients. Zuckerman *et al*.[8] reported that 18 of 33 (54 %) HCV-infected patients had hepatitis, compared with 36% of non-HCV-infected patients undergoing chemotherapy for hematologic malignancies. Ennishi *et al*.[14] reported corresponding values of 27 % and 3%, respectively. This discrepancy in the incidence of hepatitis could be due to differences in the patient populations. In the study[14] by Ennishi *et al*., 43% and 15% of patients had chronic hepatitis and LC, respectively. In HCV-infected patients who do not undergo pharmacological immunosuppression, the incidence of spontaneous hepatic flare is 2% to 40%.[15-18]

The incidence of hepatitis in patients with detectable HCV RNA was significantly high in patients with solid tumor while there was no difference when patients were grouped according to treatment modality except that the patients treated with only corticosteroids rarely experienced hepatitis. In patients at

Table 3. Univariate Analysis of Factors Related to the Enhanced Replication of HCV

	Patients with enhanced HCV replication	Patients without enhanced HCV replication	p-value*
No. of patients	9 (27)	24 (73)	
Age, yr	53±14	58±14	0.31
Male sex	3 (33)	10 (42)	0.74
Disease category			0.48
Solid tumor	3 (33)	7 (29)	0.82
Hematological tumor	3 (33)	13 (54)	0.29
Other[†]	3 (33)	4 (17)	0.30
Treatment			0.08
Hematopoietic stem cell transplantation	1 (11)	6 (25)	0.39
Autologous/allogenic	0/1	2/4	0.714
Rituximab-containing regimen	1 (11)	4 (17)	0.69
Immunosuppressive agents[‡]±corticosteroids	2 (22)	3 (13)	0.49
Corticosteroids only	1 (11)	1 (4)	0.46
Other[§]	4	10	1.00
Baseline laboratory findings			
Prothrombin time, INR	1.0±0.0	1.03±0.17	0.61
Albumin, g/dL	3.7±0.5	3.8±0.5	0.42
Total bilirubin, mg/dL	0.67±0.50	0.59±0.56	0.70
HCV RNA, IU/mL	84,200	357,500	0.88
	(2,240–6.37×10^6)	(not detected–3.46×10^7)	
Liver cirrhosis	4 (44)	1 (4)	0.004*
HBV reactivation[‖]	0/7	0/16	

Data are presented as number (%), mean±SD, or median (range).
HCV, hepatitis C virus; INR, international normalized ratio; HBV, hepatitis B virus.
*Means, median or numbers significantly different between the two groups, p-value <0.05; [†]Kidney transplant recipients (n=10), rheumatoid arthritis (n=6), inflammatory bowel disease (n=2), and other medical problems requiring treatment with immunosuppressive agents with or without corticosteroids (n=20); [‡]Azathioprine, methotrexate, cyclosporine, tacrolimus, and so forth; [§]The rest of the other treatments; [‖]HBV reactivation was evaluated in 23 patients who had follow-up results of HBV markers. Among them, 7 patients had enhanced HCV replication and 16 patients did not.

risk for hepatotoxicity, corticosteroids are relatively safe in the short-term as it can be used as a treatment for autoimmune hepatitis. However, corticosteroids can lead to hepatitis when used long-term due to causing or aggravating steatosis. Drug-induced hepatitis has been also uncommonly observed due to the use of high doses.[19-21] Hematological tumors, anti-CD20 or anti-tumor necrosis factor α may be associated with hepatitis in HCV-infected patients.[7,22-24] Rituximab, which is recognized as a major risk factor for HBV reactivation, is a chimeric monoclonal antibody against the B-cell surface antigen CD20, and it was originally classified as a nonhepatotoxic drug. The incidence of rituximab-associated hepatitis in HCV-infected patients was about 26%.[14,22] In this study, three of four patients with detectable HCV RNA levels who received rituximab-containing treatment regimens developed hepatitis. Notably, in most previous studies and this work, severe hepatitis and hepatic decompensation were rare and did not affect overall survival.[6,7,13,14,25]

In this study, enhanced HCV replication occurred in nine of the 33 patients (27%); the cumulative rate was 23% at 1 year and 30% at 2 years. Because HCV RNA was not monitored at regular intervals, the real prevalence could be higher. In previous studies, the HCV RNA level increased significantly in patients who received rituximab-containing chemotherapy regimens or corticosteroids or who underwent transarterial chemolipiodolization or HSCT.[6,7,14,26,27] However, these putative risk factors for enhanced replication HCV were not significant, possibly due to the small and heterogenous population of this study. Despite this, LC was significantly associated with enhanced HCV replication, as four of five patients with LC also had enhanced HCV replication. This is due in part to the contribution of altered immunity in the cirrhotic liver to HCV reactivation, or possibly to the profound abnormalities in B-cell phenotype and function in patients with LC.[28] However, the patients diagnosed as LC in this study had relatively good liver function. Therefore, the possible relationship between LC and viral reactivation warrants further research. We also investigated whether there

Table 4. Clinical Features of Nine Patients with Enhanced Replication of HCV

Patient	Hepatitis	Treatments for underlying diseases during or after the hepatitis episode	Disease	Treatment	Duration from start of treatment to reactivation, mo	Before treatment		After treatment		Clinical outcome
						RNA, IU/mL	ALT, U/L	RNA, IU/mL	ALT, U/L	
1	Presence	No delay or discontinuation	DLBCL	R-CHOP	7.8	68,883	47	4,428,126	225	Alive
2	Presence	No delay or discontinuation	HLH	Etoposide, cyclosporine A, steroid	7.0	3,327	7	21,188,353	73	Expired
3	Presence	No delay or discontinuation	Aplastic anemia	Allogeneic BMT, cyclosporine	8.0	159,000	29	41,000,000	92	Alive
4	Presence	Discontinuation	Colon cancer	FOLFOX	10.8	11,100	20	459,000	125	Loss of follow-up
5	Presence	No delay or discontinuation	Small cell lung cancer	Etoposide, cisplatin	5.2	22,600	15	523,000	124	Expired
6	Presence	No delay or discontinuation	Kidney transplantation	Tacrolimus, MMF	23.4	2,240	39	507,000	108	Alive
7	Absence	No delay or discontinuation	Breast cancer	Doxorubicin, cyclophosphamide	8.5	14,453	19	216,327	30	Alive
8	Absence	No delay or discontinuation	Kidney transplantation	Tacrolimus, MMF	22.0	2,780,000	9	41,900,000	13	Alive
9	Absence	No delay or discontinuation	Dermatological disease	Steroid	6.4	194,000	89	3,070,000	97	Alive

HCV, hepatitis C virus; ALT, alanine aminotransferase; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, corticosteroids; HLH, hemophagocytic lymphohistiocytosis; BMT, bone marrow transplantation; FOLFOX, leucovorin, 5-FU, oxaliplatin; MMF, mycophenolate mofetil.

were viral interactions in this cohort because previous studies reported viral replication between HBV and HCV, which usually presents as suppression of HBV replication when the HCV level was increasing.[29] There was no case of HBV reactivation in 23 patients who had more than two records of HBV serum markers.

Clinicians are inevitably concerned regarding the possibility of HCV reactivation, since we have experienced several cases of HBV reactivation which led to fatal outcome in HBV endemic area. Our findings have major clinical significance that based on the results of the current study, we would not expect a significant difference in the incidence of hepatitis in HCV-infected patients who are pharmacologically immunosuppressed compared with non-HCV-infected patients, and severe hepatitis or hepatic decompensation would not be expected during treatment for underlying diseases. Although treatments were often delayed one or two cycles, most cases were managed well conservatively. Pegylated interferon and ribavirin, previous standard treatments for HCV infection, were contraindicated in many patients due to adverse effects. Although some drug interactions might be problematic,[30] recently introduced direct-acting antivirals (DAAs) may enable concurrent treatments for underlying diseases and HCV infection in patients who are at risk for HCV reactivation. For example, recurrence of HCV infection after liver transplantation could be treated with DAAs in patients already taking immunosuppressive agents. A few reports have assessed the safety and effectiveness of concomitant treatment with systemic chemotherapy and DAAs,[31] but further studies are required to validate the results.

The major limitations of this study were that heterogeneous patients with various diseases, who also received various kinds of chemotherapy or immunosuppressive therapy, were enrolled due to the retrospective nature of the study and the small number of patients. HCV infection was occasionally neglected, as was HCV reactivation, even when HCV-infected patients developed hepatitis, which resulted in a lack of data surrounding HCV reactivation and this also hindered identification of significant risk factors for hepatitis or enhanced HCV replication. Additionally, we focused on enrolling patients who had follow-up results regarding HCV markers, which led to a lack of data about HBV markers. However, although there was a possibility of HBV reactivation, it would be unlikely to influence the results of this study.

In conclusion, enhanced HCV replication can occur to a considerable degree in patients who receive chemotherapy or immunosuppressive therapy, but it may not lead to clinically significant sequelae, such as severe hepatitis or hepatic decompensation. However, clinicians should always consider the possibility of HCV reactivation in HCV-infected patients, especially in the face of pharmacological immunosuppression. Further prospective studies on the clinical outcome of enhanced HCV replication during chemotherapy and immunosuppressive therapy are warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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All authors read and approved the final version of the manuscript. H.L.L. and S.H.B. designed the research; H.L.L., S.H.B., H.Y., H.C.N., P.S.S., S.W.L., J.W.J., J.Y.C., N.I.H., B.J.S., J.W.L., and S.K.Y. performed the research and analyzed the data; H.L.L. and S.H.B. wrote the paper.

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