Received: 24 November 2020 | Revised: 8 February 2021 | Accepted: 9 February 2021

DOI: 10.1111/cas.14846

ORIGINAL ARTICLE

Cancer Science WILEY

Prophylactic antiviral therapy for hepatitis B virus surface antigen-positive patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy

Nobuhiko Yamauchi[1] | Dai Maruyama[2] | Ilseung Choi[3] | Yoshiko Atsuta[4] | Rika Sakai[5] | Kazuho Miyashita[6] | Yukiyoshi Moriuchi[7] | Hideki Tsujimura[8] | Nobuko Kubota[9] | Go Yamamoto[10] | Tadahiko Igarashi[11] | Koji Izutsu[2] | Shinichiro Yoshida[12] | Kensuke Kojima[13] | Toshiki Uchida[14] | Yoshiko Inoue[15] | Norifumi Tsukamoto[16] | Eiichi Ohtsuka[17] | Sachiko Suzuki[18] | Yoko Inaguma[19] | Satoshi Ichikawa[20] | Hiroshi Gomyo[21] | Yoko Ushijima[22] | Kisato Nosaka[23] | Mio Kurata[4] | Yasuhito Tanaka[24,25] | Ryuzo Ueda[26] | Masashi Mizokami[27] | Shigeru Kusumoto[28]

[1]Department of Hematology, National Cancer Center East Hospital, Kashiwa, Japan

[2]Department of Hematology, National Cancer Center Hospital, Tokyo, Japan

[3]Department of Hematology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[4]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

[5]Department of Hematology and Medical Oncology, Kanagawa Cancer Center, Yokohama, Japan

[6]Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan

[7]Department of Hematology, Sasebo City General Hospital, Sasebo, Japan

[8]Division of Hematology-Oncology, Chiba Cancer Center, Chiba, Japan

[9]Department of Hematology, Saitama Cancer Center, Saitama, Japan

[10]Department of Hematology, Toranomon Hospital, Tokyo, Japan

[11]Department of Hematology, Gunma Prefectural Cancer Center, Gunma, Japan

[12]Department of Hematology, National Hospital Organization Nagasaki Medical Center, Ohmura, Japan

[13]Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan

[14]Department of Hematology and Oncology, Japanese Red Cross Nagoya Daini Hospital, Nagoya, Japan

[15]Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan

[16]Department of Hematology, Gunma University Hospital, Maebashi, Japan

[17]Department of Hematology, Oita prefectural Hospital, Oita, Japan

[18]Department of Hematology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan

[19]Division of Hematology, Fujita Health University, Toyoake, Japan

[20]Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan

[21]Division of Hematology, Hyogo Cancer Center, Akashi, Japan

[22]Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[23]Department of Hematology, Kumamoto University Hospital, Kumamoto, Japan

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ETV, entecavir; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; LAM, lamivudine; NA, nucleos(t)ide analogue; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Nobuhiko Yamauchi and Dai Maruyama contributed equally to this article.

Statement of prior presentation: This study was presented in poster form at the 60th Annual Meeting of the American Society of Hematology, San Diego, California, 3 December 2018.

[24]Department of Virology and Liver unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[25]Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[26]Department of Tumor Immunology, Aichi Medical University School of Medicine, Nagakute, Japan
[27]Genome Medical Sciences Project, National Center for Global Health and Medicine, Ichikawa, Japan
[28]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Correspondence
Shigeru Kusumoto, Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-chou, Mizuho-ku, Nagoya, Aichi 467-8601, Japan.
Email: skusumot@med.nagoya-cu.ac.jp

Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: JP20fk0210035h0003

Abstract

We conducted a nationwide retrospective analysis of 116 hepatitis B virus (HBV) surface antigen (HBsAg)-positive patients with diffuse large B-cell lymphoma (DLBCL) and 278 HBsAg-negative patients with DLBCL, as a control cohort, who received rituximab-containing regimens as an induction chemotherapy at 30 Japanese medical centers between January 2004 and December 2014. Hepatitis was defined as an absolute serum alanine aminotransferase (ALT) level of ≥100 U/L. HBV reactivation-related hepatitis was defined as hepatitis with an absolute serum HBV DNA level of ≥3.3 log IU/mL or an absolute increase of ≥2 log compared with the baseline value. HBsAg-positive patients were divided into three groups based on anti–HBV prophylactic therapy: no nucleos(t)ide analogue (non–NA, n = 9), lamivudine (LAM, n = 20), and entecavir (ETV, n = 87). The 4-year cumulative incidence (CI) of hepatitis in HBsAg-positive and HBsAg-negative patients was 21.1% and 14.6% ($P = .081$), respectively. The 4-year CI of HBV reactivation-related hepatitis was higher in HBsAg-positive patients than in HBsAg-negative patients (8.0% vs 0.4%; $P < .001$). Among HBsAg-positive patients, the 4-year CI of HBV reactivation-related hepatitis was the highest in the non–NA group (33.3%), followed by the LAM (15.0%) and ETV (3.8%) groups ($P < .001$). Of note, 3 non–NA patients (33%) and 1 LAM patient (5%) (but no ETV patients) died due to HBV hepatitis. Based on Cox multivariate analysis, HBsAg positivity was not associated with poor overall survival. Prophylactic use of ETV would reduce the occurrence of HBV reactivation-related hepatitis and mortality in HBsAg-positive DLBCL patients receiving rituximab-containing chemotherapy.

KEYWORDS
antiviral prophylaxis, B-cell lymphoma, HBsAg-positive, HBV reactivation, rituximab

1 | INTRODUCTION

Hepatitis B virus (HBV) reactivation is a well-known but potentially fatal complication in patients with seropositive for hepatitis B virus surface antigen (HBsAg) receiving systemic chemotherapy.[1,2] The highest rates of HBV reactivation are usually seen in HBsAg-positive patients with lymphoma who receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), especially in combination with the anti–CD20 monoclonal antibody rituximab.[3,4] Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell lymphoma and a combination regimen with rituximab (R) plus CHOP (R-CHOP) is considered standard first-line immunochemotherapy.[5,6] Among HBsAg-positive patients with B-cell lymphoma, the incidence of HBV reactivation after R-CHOP is reported as being from 59% to 80% if the anti–HBV nucleos(t)ide analogue (NA) therapy is not given before initiation of R-CHOP-like chemotherapy (without antiviral prophylaxis), which often leads to HBV reactivation-related hepatitis.[4,7] Moreover, HBV reactivation-related hepatitis typically results in delayed or premature discontinuation of chemotherapy and may be fatal itself. It has a negative impact on survival, especially in patients with high HBV DNA viral loads at baseline.[8]

Some studies have shown that prophylactic anti–HBV NA therapy for HBsAg-positive patients decreases the risk of HBV reactivation and subsequent hepatic events. Most of these studies address the effectiveness of prophylactic use of lamivudine, a first-generation anti–HBV NA, in HBsAg-positive patients receiving (R-)CHOP,[9,10] although long-term use of prophylactic lamivudine is associated with drug resistance mutations, which limit its long-term efficacy.[11] Entecavir (ETV), a second-generation

anti-HBV NA has stronger activity and better resistance than first-generation anti–HBV NA, is currently most widely used as prophylaxis for HBV reactivation in HBsAg-positive patients.[4] As such, several guidelines recommend the prophylactic use of anti–HBV NA. A second-generation NA (ETV or tenofovir) should be started before the initiation of chemotherapies and continued until at least 6 or 12 months after completion of chemotherapies for HBsAg-positive patients.[12,13] However, these recommendations are not supported by concrete evidence because only limited data are available regarding the effectiveness of ETV in preventing HBV reactivation in HBsAg-positive patients receiving systemic chemotherapy.[14] In particular, the clinical impact of second-generation NA against HBV reactivation and subsequent hepatitis and also on long-term outcomes has not been fully elucidated in HBsAg-positive patients with lymphoma having high HBV DNA viral loads at baseline who have been treated with R-CHOP-like chemotherapy.

For the present study, we conducted a nationwide multicenter retrospective analysis to evaluate the incidence of hepatitis and HBV reactivation-related hepatitis and the clinical outcomes of HBsAg-positive patients with DLBCL who have been uniformly treated with R-CHOP-like chemotherapy compared to HBsAg-negative patients.

2 | METHODS

2.1 | Study population and design

A total of 394 patients with DLBCL who received R-CHOP-like chemotherapy were enrolled in this retrospective study. The study included 116 HBsAg-positive patients with DLBCL as well as 278 HBsAg-negative patients with DLBCL (as a control) who were diagnosed within 2 months (1 month before or after) of the diagnosis date of each patient who was included among those HBsAg-positive patients, across 30 Japanese medical centers (Figure S1). Adult patients (aged ≥20 years) with untreated DLBCL (including transformed DLBCL from low-grade B-cell lymphoma) who had a baseline HBV serostatus at diagnosis of DLBCL, then received at least one cycle of R-CHOP or R plus pirarubicin, cyclophosphamide, vincristine, and prednisone (R-THP-COP) regimen as an initial chemotherapy between January 2004 and December 2014 were included. Diagnosis of DLBCL was based on local hematopathologists in accordance with the World Health Organization (WHO) classification. HBsAg-negative patients who were seropositive for antibodies against hepatitis B core antigen (anti–HBc) and/or antibodies against HBsAg (anti–HBs) were also included. Patients who met any of the following criteria were excluded from the study: seropositive for hepatitis C virus or human immunodeficiency virus, alanine transaminase (ALT) level ≥100 U/L before R-CHOP-like chemotherapy, DLBCL with central nervous system involvement, primary testicular lymphoma, intravascular large-cell lymphoma, a previous history of chemotherapy, and a previous history of decompensated cirrhosis or hepatocellular carcinoma. The decision to provide NA was based on the individual preferences of the treating physicians and/or patients. Medical records were reviewed for baseline characteristics, details of chemotherapy regimens, liver function tests, HBV DNA levels, HBV-related events, and survival. All data were collected with local institutional review board approval and complied with all provisions of the Declaration of Helsinki.

2.2 | Lymphoma staging and response assessment

The Ann Arbor classification and the 1999 Cotswold modifications were used to evaluate disease stage. Response was assessed after completing initial R-CHOP-like chemotherapy according to the International Workshop Response Criteria (1999).[15] Among the patients who received computed tomography (CT) and/or positron emission tomography (PET)/CT with [18F]-fluorodeoxyglucose imaging, the response was assessed according to the revised response criteria for malignant lymphoma 2007.[16]

2.3 | Liver function tests and hepatitis B virus markers

Each patient underwent a series of liver function tests, including ALT and prothrombin time (PT). HBV-related markers, including HBV serostatus and HBV DNA levels, from the diagnosis of DLBCL to the last follow up were queried. HBsAg positivity was determined based on the serological results of HBsAg that were measured at each institution before the initiation of systemic chemotherapy for DLBCL (detection methods of HBsAg were not defined). Similarly, detection methods for anti–HBs and anti–HBc were not defined. Each serum HBV DNA level was recalculated using log IU/mL. Hepatitis was defined as an absolute serum ALT level of ≥100 U/L. Severity of hepatitis was determined based on the highest ALT value during the observed period using Common Terminology Criteria for Adverse Events version 4.0. HBV reactivation-related hepatitis was defined as the presence of hepatitis together with an absolute serum HBV DNA level of ≥3.3 log IU/mL or an absolute increase of ≥2 log compared with baseline value. Serum HBV DNA levels were measured using a quantitative PCR assay, available at each medical center. HBV reactivation-related fulminant hepatitis was defined as the presence of HBV reactivation-related hepatitis accompanied by mild to severe encephalitis and prolonged PT (>40%). Patients were diagnosed as having cirrhosis if they had at least one of the representative CT findings (ie, hypertrophy of the left lobe with concomitant atrophy of the right lobe, surface nodularity, and portosystemic collaterals). Severity of cirrhosis was determined according to the Child-Pugh classification, where decompensated cirrhosis was defined as having Child-Pugh B (7-9 points) or C (10-15 points).

2.4 | End points

The primary endpoint of the present study was the cumulative incidence of hepatitis (defined as an absolute serum ALT level of ≥100 U/L) in HBsAg-positive and HBsAg-negative patients. Secondary endpoints were the cumulative incidence of hepatic events, which comprised the cumulative incidence of HBV reactivation-related hepatitis, the cumulative incidence of HBV reactivation-related fulminant hepatitis, the cumulative incidence of decompensated cirrhosis and hepatocellular carcinoma, and response to R-CHOP-like chemotherapy. Response to R-CHOP-like chemotherapy included the overall response rate (ORR), complete response (CR) rate, and survival (ie, the cumulative incidence of death due to HBV reactivation-related hepatitis, progression free survival [PFS], and overall survival [OS]).

2.5 | Statistical analysis

Categorial variables were assessed using the χ^2-test, the Fisher exact test, and the Kruskal-Wallis test as indicated. Time to hepatitis was defined as the time from diagnosis of DLBCL to the first development of hepatitis. Patients without hepatitis were censored at the time of their last ALT assessment. Time to hepatitis was estimated using cumulative incidence methods and compared between HBsAg-positive patients and HBsAg-negative patients using the Gray's test. A competing event was defined as death before the occurrence of hepatitis. PFS was defined as the time from diagnosis of DLBCL to the date of documented disease progression, relapse, or death from any cause. OS was defined as the time from diagnosis of DLBCL to death from any cause or the last follow up. OS and PFS were estimated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate prognostic factors for OS were assessed using Cox proportional hazards analysis. All statistical tests were two-sided, and $P < .05$ was considered statistically significant. Statistical analysis was performed using the Stata software version 13.1 (StataCorp LLC) and EZR 1.35[17] at the Japanese Data Center for Hematopoietic Cell Transplantation.

3 | RESULTS

3.1 | Patient characteristics

All baseline characteristics, except for HBV status, were similar between HBsAg-positive and HBsAg-negative patients (Table 1). R-CHOP was the most commonly used regimen (n = 337, 85.5%), followed by R-THP-COP (n = 57, 14.5%). HBsAg-positive patients with detectable and quantifiable HBV DNA (n = 65, 56.0%) had a median baseline HBV DNA level of 2.9 l

og IU/mL (interquartile range [IQR]; 2.0-3.7). Among HBsAg-positive patients, 5 (4.3%) had compensated cirrhosis (patients with decompensated cirrhosis were excluded from the present study). HBsAg-positive patients were allocated into three groups based on prophylactic NA therapy: no prophylactic therapy (non–NA, n = 9), prophylactic therapy with lamivudine (LAM, n = 20), and prophylactic therapy with ETV (n = 87). Among HBsAg-negative patients, 64 (23.0%) patients were seropositive for anti–HBc or anti–HBs. Both R-CHOP and R-THP-COP were performed for a median of six cycles (IQR, 5-8). Median follow-up times were 4.3 and 4.5 years in HBsAg-positive and HBsAg-negative patients, respectively. The median duration of prophylactic NAT was 2.5 years (IQR, 1.1-4.8 years) in LAM and 3.4 years (IQR, 1.3-5.1) in ETV patients. Among 9 patients in the non–NA group, 2 patients started prophylactic ETV immediately after the initiation of systemic chemotherapy and another 5 patients started NA upon the occurrence of hepatitis (3 patients received lamivudine and 2 patients received ETV). The remaining 2 patients had not received any NA therapy during the observation period and did not develop hepatitis.

3.2 | Hepatitis

The 4-year cumulative incidence of hepatitis was 21.1% (95% confidence interval [CI]: 14.1%-28.9%) and 14.6% (95% CI: 10.7%-19.2%) in HBsAg-positive and HBsAg-negative patients, respectively ($P = .081$) (the number of patients who developed hepatitis was 28 and 42 in HBsAg-positive and HBs-negative groups, respectively) (Figure 1A). HBsAg-positive patients had a higher frequency of grade 3-4 hepatitis compared with HBsAg-negative patients (16.3% vs 7.2%) ($P = .027$). Among HBsAg-positive patients, the 4-year cumulative incidence of hepatitis was the highest for non–NA (77.8%, 95% CI: 36.5%-93.9%), followed by LAM (20.0%, 95% CI: 6.2%-39.3%) and ETV patients (15.4%, 95% CI: 8.7%-23.9%) (the number of patients who developed hepatitis was 7, 6, and 15 in non–NA, LAM, and ETV groups, respectively) (Figure 1B). The incidence of grade 3-4 hepatitis was the highest in non–NA (55.5%), followed by LAM (25.0%) and ETV patients (10.4%) ($P < .001$).

3.3 | Hepatitis B virus reactivation-related hepatic events

Hepatitis B virus surface antigen-positive patients had a higher 4-year cumulative incidence of HBV reactivation-related hepatitis compared with HBsAg-negative patients (8.0%, 95% CI: 3.9%-14.0% vs 0.4%, 95% CI: 0.0%-2.0%, $P < .001$, Figure 2A) (the number of patients who developed HBV reactivation-related hepatitis was 10 and 1 in HBsAg-positive and HBsAg-negative groups, respectively). Importantly, the 4-year cumulative incidence of HBV reactivation-related hepatitis among HBsAg-positive patients was the highest in non–NA (33.3%, 95% CI: 7.8%-62.3%), followed by LAM (15.0%, 95% CI: 3.7%-33.5%), and ETV patients (3.8%, 95% CI: 1.0%-9.8%) ($P < .001$) (Figure 2B).

Details of 10 HBsAg-positive patients with HBV reactivation-related hepatitis are shown in Table 2. Notably, HBV reactivation-related hepatitis occurred early after initiation of R-CHOP-like

TABLE 1 Baseline characteristics, HBV status, and lymphoma treatment of HBsAg-positive and HBsAg-negative patients

Characteristic	HBsAg-positive patients (n = 116)	HBsAg-negative patients (n = 278)	*P*-value
Median age, y (IQR)	64 (59-70.5)	66 (58-74)	.323
Gender, n (%)			
Male/Female	66/50 (56.9/43.1)	140/138 (50.4/49.6)	.269
ECOG performance status, n (%)			
0	45 (38.8)	143 (51.4)	.051
1	48 (41.4)	86 (30.9)	
2	14 (12.1)	31 (11.2)	
3	8 (6.9)	14 (5.0)	
4	1 (0.9)	4 (1.4)	
Clinical stage, n (%)			
I	31 (26.7)	62 (22.3)	.753
II	31 (26.7)	95 (34.2)	
III	28 (24.1)	52 (18.7)	
IV	26 (22.4)	69 (24.8)	
Hepatic involvement, n (%)	4 (3.5)	9 (3.2)	.796
Prognostic factor (IPI), n (%)			
0-1	40 (34.5)	112 (40.3)	.389
2	32 (27.6)	70 (25.2)	
3	23 (19.8)	46 (16.6)	
4-5	21 (18.1)	50 (18.0)	
HBV serostatus, n (%)			
HBeAg +/−/ND	7/84/25 (6.0/72.4/21.6)	—	—
Anti−HBc+ and/or anti−HBs+	—	64 (23.0)	
HBV DNA levels			
Undetectable, n (%)	26 (22.4)	—	—
Detectable but not quantifiable, n (%)	6 (5.2)	—	
Quantifiable,[a] n (%)	65 (56.0)	—	
Median HBV DNA level (IQR)	2.9 IU/mL (2.0-3.7)		
Not determined, n (%)	19 (16.4)	—	
Cirrhosis, n (%)	5 (4.3)	—	—
Prophylactic nucleoside analogue herapy			
No prophylactic therapy, n (%)	9 (7.8)	—	—
Lamivudine, n (%)	20 (17.2)	—	
Median dose (IQR)	100 mg/d (100-100)		
Entecavir, n (%)	87 (75.0)	—	
Median dose (IQR)	0.5 mg/d (0.5-0.5)		
Initial treatment			
R-CHOP, n (%)	99 (85.3)	238 (85.7)	—
Median cycles (IQR)	6 (6-8)	6 (6-8)	
R-THP-COP, n (%)	17 (14.7)	40 (14.4)	
Median cycles (IQR)	6 (5-8)	6 (6-8)	

Anti−HBc, antibodies against hepatitis B core antigen; anti−HBs, antibodies against hepatitis B surface antigen; ECOG, Eastern Cooperative Oncology Group; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IPI, international prognostic index; IQR, interquartile range; ND, not determined; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; THP-COP, rituximab, pirarubicin, cyclophosphamide, vincristine and prednisone.

[a]Data missing n = 2.

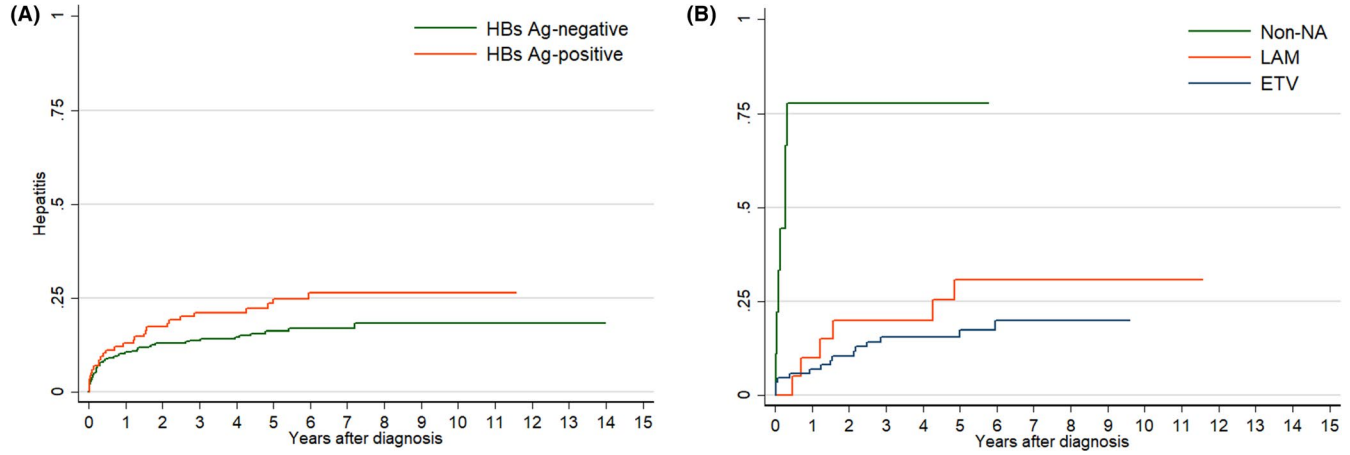

FIGURE 1 Cumulative incidence of hepatitis. A, Cumulative incidence of hepatitis in hepatitis B virus (HBV) surface antigen (HBsAg)-positive and HBsAg-negative patients with diffuse large B-cell lymphoma (DLBCL) who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-like chemotherapy. B, Cumulative incidence of hepatitis among HBsAg-positive patients; comparison of those patients who received entecavir (ETV) or lamivudine (LAM) as anti–HBV prophylaxis, and who did not receive anti–HBV nucleos(t)ide analogue (non–NA)

chemotherapy: within less than 6 months in patients without antiviral prophylaxis or with lamivudine prophylaxis (Patients 1-4 in Table 2). Two patients with lamivudine prophylaxis experienced breakthrough reactivation; HBV reactivation-related hepatitis developed during antiviral prophylaxis (Patients 4 and 5; Patient 4 had YMDD mutation in Table 2). Furthermore, the remaining 2 patients with lamivudine prophylaxis and 3 patients with ETV prophylaxis experienced HBV reactivation-related hepatitis after the withdrawal of NA therapy (Patients 6-10; including delayed HBV reactivation, Patients 7-10 in Table 2).

The 4-year cumulative incidence of HBV reactivation-related fulminant hepatitis was 11.1% (95% CI: 0.6%-38.8%) in non–NA patients, which was higher compared with LAM (5.0%, 95% CI: 0.3%-20.5%) and in ETV patients (0.0%) ($P = .025$) (Figure S2A) (the number of patients who developed HBV reactivation-related fulminant hepatitis was 1 each in the non–NA and LAM groups, respectively), although none of the HBsAg-negative patients were diagnosed with HBV reactivation-related fulminant hepatitis.

The 4-year cumulative incidence of decompensated cirrhosis was 11.1% (95% CI: 0.6%-38.8%) in non–NA, which was higher than in LAM (0.0%) and in ETV (1.2%, 95% CI: 0.1%-5.6%) ($P = .167$) (the number of patients who developed decompensated cirrhosis was 1 each in non–NA and ETV groups, respectively) (Figure S2B). The 4-year cumulative incidence of hepatocellular carcinoma was 0.0%, 5.3% (95% CI: 0.4%-21.5%), and 0.0% in non–NA, LAM and ETV patients, respectively (Figure S2C) (the number of patients who developed hepatocellular carcinoma was 1 in the LAM group).

The 4-year cumulative incidence of death due to HBV reactivation-related hepatitis was 3.5% (95% CI: 1.1%-8.0%) and 0.4% (95% CI: 0%-2.0%) in HBsAg-positive and HBsAg-negative patients ($P = .014$) (Figure 2C) (the number of patients who died from HBV reactivation-related hepatitis was 4 and 2 in HBsAg-positive and HBsAg-negative groups, respectively). Importantly, among HBsAg-positive patients, the 4-year cumulative incidence of death due to HBV reactivation-related hepatitis was highest in non–NA (33.3%, 95% CI: 7.8%-62.3%), followed by LAM (5.0%, 95% CI: 0.3%-20.5%) and ETV patients (0%) (the number of patients who died from HBV reactivation-related hepatitis was 3 and 1 in non–NA and LAM groups, respectively). Of note, no patients in the ETV group died of HBV reactivation-related hepatitis (Patients 8-10 in Table 2; Figure 2D).

3.4 | Response to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone-like chemotherapy

The ORR and CR rates were similar between HBsAg-positive and -negative patients (ORR: 97.4% in HBsAg-positive patients vs 92.5% in HBsAg-negative patients, $P = .066$, CR rate: 89.7% in HBsAg-positive patients vs 83.8% in HBsAg-negative patients, $P = .158$).

3.5 | Survival analysis

The 4-year unadjusted OS rate was 77.5% (95% CI: 68.5%-84.2%) in HBsAg-positive patients and was similar in HBsAg-negative patients (82.2%, 95% CI: 77.0%-86.4%) ($P = .330$) (Figure 3A). Among HBsAg-positive patients, the 4-year unadjusted OS was poor in non–NA (55.6%, 95% CI: 20.4%-80.5%), compared with LAM (84.7%, 95% CI: 59.7%-94.8%) and ETV (78.0%, 95% CI: 67.3%-85.5%) ($P = .049$) (Figure 3B). Based on multivariate analysis, when including older age, advanced stage, performance status, elevated lactate dehydrogenase (LDH), number of extranodal sites, female (vs male), and HBsAg-positive (vs HBsAg-negative) as covariates, HBsAg-positive status was not significantly associated with poor OS (Table 3). Overall, 33 patients among the HBsAg-positive patients and 62 among the HBsAg-negative patients died during follow up. Lymphoma was the most common cause of death in both HBsAg-positive (n = 13) and HBsAg-negative patients (n = 38).

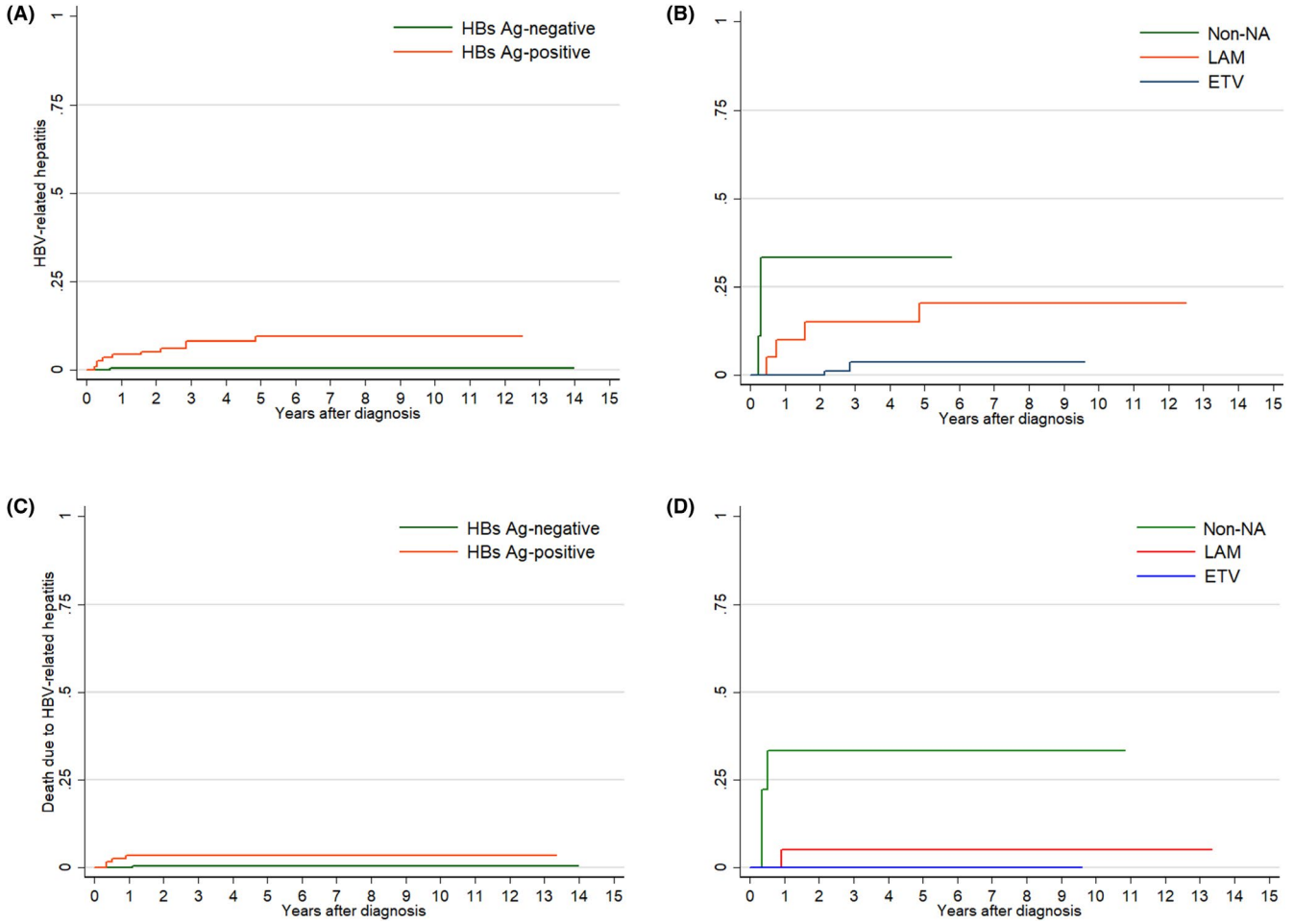

FIGURE 2 Cumulative incidence of hepatitis B virus (HBV) surface antigen (HBsAg) reactivation-related hepatitis or death. A, Cumulative incidence of HBV reactivation-related hepatitis in HBsAg-positive and HBsAg-negative patients with diffuse large B-cell lymphoma (DLBCL) who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-like chemotherapy. B, Cumulative incidence of HBV reactivation-related hepatitis among HBsAg-positive patients; comparison of those patients who received entecavir (ETV) and lamivudine (LAM) as anti–HBV prophylaxis, and who did not receive anti–HBV nucleos(t)ide analogue (non–NA). C, Cumulative incidence of death due to HBV reactivation-related hepatitis in HBsAg-positive and HBsAg-negative patients. D, Cumulative incidence of death due to HBV reactivation-related hepatitis among HBsAg-positive patients; comparison of ETV, LAM, and non–NA

The 4-year PFS was 66.8% (95% CI: 57.1%-74.7%) in HBsAg-positive patients and was comparable with that in HBsAg-negative patients (73.7%, 95% CI: 67.8%-78.6%) ($P = .321$) (Figure 3C). Among HBsAg-positive patients, the 4-year PFS was poor in non–NA (44.4%, 95% CI: 13.6%-71.9%), compared with LAM (79.7%, 95% CI: 54.5%-91.9%) and ETV patients (66.0%, 95% CI: 54.6%-75.2%) ($P = .047$) (Figure 3D).

3.6 | Patients with high hepatitis B virus DNA viral loads at baseline

Among HBsAg-positive patients, 49 had higher baseline serum HBV DNA (3.0 log copies/mL or more, approximately 2.2 log IU/mL or more) at baseline. Among those patients, 2, 7, and 40 underwent non–NA, lamivudine prophylaxis, and ETV prophylaxis, respectively. Two patients who had non–NA or lamivudine prophylaxis developed fulminant hepatitis, which finally resulted in decompensated cirrhosis. No patients with ETV prophylaxis developed fulminant hepatitis or cirrhosis during the study period. These patients had similar OS when compared with the remaining patients ($P = .992$) (Figure S3A). In addition, steroid use as a part of R-CHOP-like chemotherapy was not associated with worse overall survival ($P = .468$) in patients with higher baseline serum HBV DNA (Figure S3B). Of note, no patients with ETV prophylaxis died of HBV reactivation-related complications during the study period.

4 | DISCUSSION

Our multicenter retrospective study had the following two important findings. First, prophylactic use of ETV in HBsAg-positive

TABLE 2 Baseline characteristics and clinical course for the 10 HBsAg-positive patients with HBV reactivation-related hepatitis

Pt	Age, y	Gender	Chemotherapy regimen	Antiviral prophylaxis	ALT, IU/L		HBV DNA, log IU/mL	
					Baseline	Peak level	Baseline	Peak level
1	61	M	R-CHOP	no	34	134	4.2	6.4
2	70	M	R-THP-COP	no	11	1770	ND	6.8
3	72	F	R-THP-COP	no	13	826	ND	6.9
4	82	M	R-THP-COP	LAM	2	170	3.4	6.3
5	78	M	R-THP-COP	LAM	16	337	UD	7.3
6	40	M	R-CHOP	LAM	20	1544	4.1	6.9
7	65	M	R-CHOP	LAM	58	301	ND	5.7
8	47	M	R-CHOP	ETV	22	331	>9.1	3.6
9	63	M	R-CHOP	ETV	18	184	3.2	4.9
10	61	F	R-CHOP	ETV	24	2687	2.5	4.6

ALT, alanine transaminase; ETV, entecavir; F, female; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; M, male; NA, nucleos(t)ide analogue; ND, not determined; Pt, patient; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-THP-COP, rituximab, pirarubicin, cyclophosphamide, vincristine and prednisone; UD, undetectable.

[a]Still alive at the data-cutoff date.

[b]ETV was discontinued because of intestinal pneumonia.

patients who were treated with R-CHOP-like chemotherapy significantly reduced the incidence of hepatitis (4-year cumulative incidence rate: 77.8% in non–NA, 20.0% in LAM, 15.4% in ETV) as well as that of HBV reactivation-related hepatitis (4-year cumulative incidence rate: 33.3% in non–NA, 15.0% in LAM, and 3.8% in ETV patients) and subsequent hepatic events, including fulminant hepatitis and decompensated cirrhosis. Second, prophylactic use of ETV could completely prevent death associated with HBV reactivation-related hepatitis in HBsAg-positive patients with DLBCL who were treated with R-CHOP-like chemotherapy (4-year cumulative incidence rate: 33.3% in non–NA, 5.0% in LAM, and 0% in ETV patients), even in those with high HBV DNA viral loads. Although there was some selection bias, in the present study, HBsAg-positivity had no negative impact on OS in DLBCL patients treated with R-CHOP-like chemotherapy if they had received prophylactic ETV.

A meta-analysis comparing the incidence of hepatitis between patients receiving lamivudine prophylaxis and patients not receiving antiviral prophylaxis revealed that lamivudine prophylaxis significantly decreased the incidence of hepatitis (RR = 0.40, 95% CI: 0.26-0.63, $P < .001$).[18] In the present study, prophylactic use of ETV as well as lamivudine significantly decreased the incidence of hepatitis, which was comparable to that of HBsAg-negative patients. In non–NA, 7 patients out of 9 patients (77.8%) developed hepatitis within 6 months of initiation of R-CHOP-like chemotherapy. Among these 7 patients, 3 patients developed HBV reactivation-related hepatitis and the remaining 4 were diagnosed as having drug-related hepatitis. It was difficult to identify the risk factors for HBV reactivation-related hepatitis in the non–NA group because of the limited number of patients.

In the pre–rituximab era, HBsAg-positive lymphoma patients receiving chemotherapy had already been considered to be at high risk of HBV reactivation and 24%-53% of these patients experienced HBV reactivation after chemotherapy without prophylactic NA therapy.[3] In the rituximab era, some studies reported that HBsAg-positive lymphoma patients receiving R-CHOP-like chemotherapy had the highest risk of developing HBV reactivation, with the incidence rate being as high as 59%-80%, if prophylactic NA therapy was not initiated.[4,7] After the introduction of lamivudine, several studies, including two randomized controlled trials, revealed that prophylactic use of lamivudine significantly reduced the incidence of HBV reactivation in patients with lymphoma receiving R-CHOP-like chemotherapy (4.6%-55.4% in patients with lamivudine prophylaxis and 24.4%-85.4% in patients not receiving prophylactic NA therapy).[9,19] However, HBV reactivation occurs in a fraction of patients receiving prophylactic lamivudine because long-term use of prophylactic lamivudine is associated with drug resistance.[20] Conversely, ETV, a second-generation NA with a higher barrier to resistance (compared with lamivudine), is currently the most commonly used NA for prophylaxis and preemptive therapy for HBV reactivation. However, apart from one randomized study, the evidence is scarce regarding the advantages of ETV over lamivudine as prophylaxis for HBV reactivation in HBsAg-positive lymphoma patients treated with R-CHOP-like chemotherapy.[21] In that study, HBsAg-positive patients (n = 121) with DLBCL receiving R-CHOP were randomized to ETV or lamivudine for the prophylaxis against HBV reactivation. Patients with abnormal liver function tests or serum HBV DNA levels of >3.0 log copies/mL (approximately 2.2 log IU/mL) were excluded. The incidence of HBV reactivation-related hepatitis was significantly lower in the ETV group than in the lamivudine group (0% vs 13.3%; $P = .003$). Importantly, patients with high HBV DNA viral loads at baseline in the present study who had ETV prophylaxis had significantly lower risk of HBV reactivation-related hepatitis than patients who had lamivudine prophylaxis and patients who had no prophylaxis.

Time from initiation of chemotherapy to HBV-related hepatitis, mo	Time from NA therapy withdrawal to HBV-related hepatitis, mo	Survival outcome	Overall survival time, mo	Cause of death
2	—	Death	130	Gastric cancer
3	—	Death	6	HBV reactivation
3	—	Death	4	HBV reactivation
5	During LAM therapy	Death	64	Unknown
18	During LAM therapy	Death	38	Pneumonia
8	2	Death	10	HBV reactivation
57	1	Alive	160+[a]	—
33	1[b]	Death	35	Colorectal cancer
33	20	Alive	63+[a]	—
25	7	Alive	61+[a]	—

Overall, 10 patients developed HBV reactivation-related hepatitis (3 in non–NA, 4 in LAM, and 3 in ETV) during the study period. Breakthrough HBV reactivation occurred in 2 of 4 patients with lamivudine prophylaxis but in none of 3 patients with ETV prophylaxis. Interestingly, HBV reactivation-related hepatitis occurred in 2 out of 5 patients who received prolonged NA therapy (>2 years) after completing R-CHOP-like chemotherapy. Similar findings were reported in the abovementioned randomized study, in which 5 patients among patients (8.3%) who had received lamivudine for prophylaxis experienced HBV reactivation after stopping lamivudine. Based on these findings, the optimal duration of prophylactic NA therapy may differ for virological or serological status, and periodic HBV DNA should be monitored to prevent HBV reactivation-related hepatitis at least 1 year after antiviral prophylaxis if antiviral prophylaxis is withdrawn.

In a large cohort study, baseline HBV DNA levels were shown to be associated with long-term risk of progression to liver cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B, regardless of whether they are receiving chemotherapy.[22] Chemotherapy-induced HBV reactivation may increase the risk of these hepatic complications in HBsAg-positive patients. However, to date, there is scarce evidence regarding the efficacy of prophylactic NA therapy in this situation as long-term follow up is necessary to reveal whether prophylactic NA therapy reduces the risk of these hepatic complications in HBsAg-positive patients, especially in patients with high HBV DNA viral loads such as ≥2.2 log IU/mL at baseline. In the present study with median HBV DNA levels of 2.9 log IU/mL in the patients with baseline HBV DNA measurements (n = 97, 84%), no patients with ETV prophylaxis developed fulminant hepatitis or cirrhosis during the study period irrespective of steroid use being a part of R-CHOP-like chemotherapy; in contrast, 2 patients who had no prophylaxis or lamivudine prophylaxis developed fulminant hepatitis, which resulted in decompensated cirrhosis, although these findings could not be used to reach a definitive conclusion, partly because of the small sample size and the limitation of the retrospective study design.

Previous studies have reported that patients receiving lamivudine prophylaxis had a significantly reduced rate of overall mortality and mortality due to HBV reactivation compared with patients without NA therapy.[9,10] However, there is also limited evidence of whether ETV prophylaxis may further reduce the rate of overall mortality and mortality due to HBV reactivation. In line with the previous studies, our patients who received lamivudine or ETV prophylaxis had better OS compared with those not receiving NA therapy, which was similar to the results for HBsAg-negative patients. We could not assess the difference in OS between ETV and LAM groups due to the small sample sizes of these subgroups.

Several immunochemotherapy regimens other than R-CHOP have also been widely used for treatment of lymphoma patients. Among them, obinutuzumab, a newer generation of anti–CD20 monoclonal antibody, is used for treatment of follicular lymphoma, in combination with CHOP or bendamustine; however, HBsAg-positive patients were excluded from a pivotal study.[23] Furthermore, HBsAg-positive patients treated with mogamulizumab[24] (a monoclonal antibody targeting the C-C chemokine receptor 4) or nivolumab or pembrolizumab[25] (monoclonal antibodies targeting programmed death-1) have been considered to be at potentially high risk of HBV reactivation; however, to date, no studies have addressed this topic. Further studies are needed to estimate the risk and incidence of HBV reactivation for HBs-positive patients treated with these novel agents that can enhance immune response for solid or hematological malignancies.

While our data provide novel findings regarding the effectiveness of ETV in HBsAg-positive DLBCL patients treated with

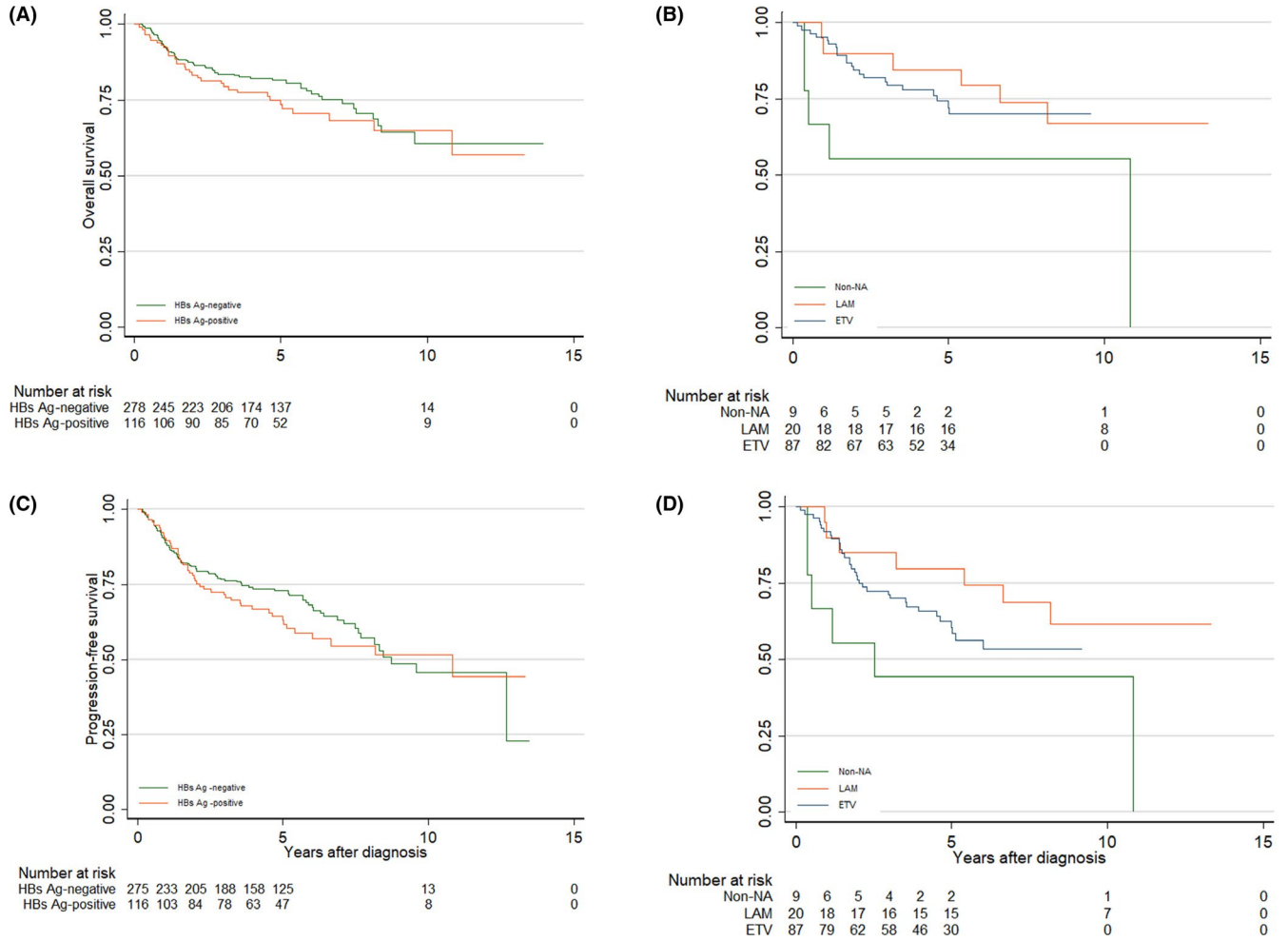

FIGURE 3 Kaplan-Meier estimate of overall survival (OS) and progression free survival (PFS). A, Kaplan-Meier estimate of OS in hepatitis B virus (HBV) surface antigen (HBsAg)-positive and HBsAg-negative patients with diffuse large B-cell lymphoma (DLBCL) who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-like chemotherapy. B, Kaplan-Meier estimate of OS among HBsAg-positive patients; comparison of those patients who received entecavir (ETV) or lamivudine (LAM), and who did not receive anti–HBV nucleos(t)ide analogue (non–NA). C, Kaplan-Meier estimate of PFS in HBsAg-positive and HBsAg-negative patients. D, Kaplan-Meier estimate of PFS among HBsAg-positive patients; comparison of ETV, LAM, and non–NA

TABLE 3 Prognostic factors for overall survival in 394 patients with DLBCL who received R-CHOP-like regimens

	Univariate			Multivariate		
Variables[a]	Crude HR	95% CI	*P*-value	Adjusted HR	95%CI	*P*-value
Age[b] (>60 vs **≤60**)	2.64	1.56-4.47	<.001	2.47	1.45-4.19	.001
Stage[b] (advanced stage vs **limited stage**)	1.99	1.32-2.99	.001	1.23	0.76-1.99	.393
ECOG PS[b] (>1 vs **0-1**)	3.03	1.99-4.62	<.001	1.88	1.18-3.00	.008
LDH[b] (>upper normal limit vs **≤upper normal limit**)	2.94	1.84-4.70	<.001	2.05	1.23-3.40	.006
Number of extranodal sites[b] (>1 vs **0-1**)	2.13	1.36-3.32	.001	1.51	0.92-2.48	.105
Gender (male vs **female**)	1.17	0.78-1.75	.447	1.23	0.82-1.85	.324
HBsAg[b] (positive vs **negative**)	1.22	0.80-1.86	.350	1.20	0.79-1.84	.397

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B virus surface antigen. HR, hazard ratio; LDH, lactate dehydrogenase; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a]Reference groups for each factor are shown in bold.

[b]Variable obtained at baseline.

R-CHOP-like chemotherapy, some limitations of our study should be addressed. First, unrecognized selection biases might have been introduced because this is a retrospective study including patients from many institutions and also because we only included those HBsAg-negative patients who were diagnosed within 2 months of the diagnosis date of each HBsAg-positive patient. Second, in the present study, HBV-reactivation related hepatitis was defined as having hepatitis accompanied by serum HBV DNA elevation, because not all HBsAg-positive patients underwent routine serum HBV DNA monitoring. This definition might have led to an underestimation of the incidence of HBV reactivation-related hepatitis, although the incidence of HBV reactivation-related hepatitis was similar to that in previous studies.

In conclusion, prophylactic use of ETV reduced the occurrence of HBV reactivation-related hepatitis and reduced deaths associated with HBV reactivation-related hepatitis in HBsAg-positive patients with DLBCL treated with R-CHOP-like chemotherapy. These findings strongly support the prophylactic use of ETV in HBsAg-positive patients, including in patients with high HBV DNA viral loads at baseline. Further studies are required to determine the efficacy of other novel NA (tenofovir) therapies and to determine the optimal duration of prophylactic NA therapy in HBsAg-positive patients receiving not only anti–CD20 antibody-containing chemotherapy but also other immunochemotherapy.

ACKNOWLEDGMENTS

This research was supported by the Japan Agency for Medical Research and Development under Grant Number JP20fk0210035h0003.

DISCLOSURE

Dai Maruyama reports personal fees and grants from Ono Pharmaceutical, personal fees and grants from Celgene, personal fees and grants from Takeda Pharmaceutical, personal fees and grants from Janssen Pharmaceutical, personal fees from Eisai, personal fees and grants from Chugai Pharmaceutical, personal fees from Kyowa Kirin, personal fees from Zenyaku Kogyo Company, personal fees and grants from Bristol-Myers Squibb, personal fees from Synmosa Biopharma, personal fees from Nippon Sinyaku, grants from Merck, grants from Amgen Astellas BioPharma, grants from Astellas Pharma, grants from Sanofi, grants from Novartis Pharma, grants from Otsuka Pharmaceutical, outside the submitted work. Yoshiko Atsuta reports lecture fees from Astellas Pharma, Mochida Pharmaceutical, Meiji Seika Pharma, Chugai Pharmaceutical, Kyowa Kirin, and Janssen Pharmaceutical. Rika Sakai reports grants and personal fees from Chugai Pharmaceutical, grants and personal fees from Kyowa Kirin, grants and personal fees from Ono Pharmaceuticals, grants from Taiho Pharma, personal fees from Eisai, personal fees from Takeda, personal fees from Janssen, personal fees from Celgene, personal fees from Mundipharma, and personal fees from Nippon Shinyaku. Koji Izutsu reports grants and personal fees from Kyowa Kirin, personal fees from Chugai Pharmaceutical. Kensuke Kojima reports honoraria from Janssen. Kisato Nosaka reports personal fees from Celgene. Yasuhito Tanaka reports grants and personal fees from Fujirebio, grants and personal fees from Gilead Sciences, grants and personal fees from Bristol-Meyers Squibb, grants and personal fees from Chugai, grants and personal fees from Glaxosmithkline, grants from Fujifilim, grants from Janssen, grants from Stanford Junior University, and personal fees from Sysmex. Ryuzo Ueda reports research funding from Chugai Pharmaceutical, Kyowa Kirin, and Ono Pharmaceutical. Masashi Mizokami reports honoraria from Gilead Sciences, Sysmex. Shigeru Kusumoto reports research funding and honoraria from Chugai Pharmaceutical, research funding, and honoraria from Kyowa Kirin.

ORCID

Dai Maruyama https://orcid.org/0000-0003-0654-6920
Kisato Nosaka https://orcid.org/0000-0001-6682-2451
Shigeru Kusumoto https://orcid.org/0000-0001-6546-1279

REFERENCES

1. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol*. 2014;11:209-219.
2. Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. *Int J Hematol*. 2009;90:13-23.
3. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol*. 2009;27:605-611.
4. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer*. 2013;49:3486-3496.
5. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235-242.
6. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-4126.
7. Pei SN, Ma MC, Wang MC, et al. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. *Ann Hematol*. 2012;91:1007-1012.
8. Lau GK, Leung YH, Fong DY, et al. High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation. *Blood*. 2002;99:2324-2330.
9. Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non–Hodgkin's lymphoma: a randomized trial. *Hepatology*. 2008;47:844-853.
10. Ziakas PD, Karsaliakos P, Mylonakis E. Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. *Haematologica*. 2009;94:998-1005.
11. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. *Hepatology*. 2009;49:1503-1514.
12. Law MF, Ho R, Cheung CK, et al. Prevention and management of hepatitis B virus reactivation in patients with hematological

malignancies treated with anticancer therapy. *World J Gastroenterol*. 2016;22:6484-6500.
13. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370-398.
14. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA*. 2014;312:2521-2530.
15. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non–Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244.
16. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579-586.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-458.
18. Li H, Zhang H, Chen L, et al. Prophylactic lamivudine to improve the outcome of HBsAg-positive lymphoma patients during chemotherapy: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2015;39:80-92.
19. Yeo W, Chan PK, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol*. 2004;22:927-934.
20. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354:1001-1010.
21. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA*. 2014;312:57-67.
22. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295:65-73.
23. Kusumoto S, Arcaini L, Hong X, et al. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. *Blood*. 2019;133:137-146.
24. Ifuku H, Kusumoto S, Tanaka Y, et al. Fatal reactivation of hepatitis B virus infection in a patient with adult T-cell leukemia-lymphoma receiving the anti–CC chemokine receptor 4 antibody mogamulizumab. *Hepatol Res*. 2015;45:1363-1367.
25. Zhang X, Zhou Y, Chen C, et al. Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. *J Immunother Cancer*. 2019;7:322.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Yamauchi N, Maruyama D, Choi I, et al. Prophylactic antiviral therapy for hepatitis B virus surface antigen-positive patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy. *Cancer Sci*. 2021;112:1943–1954. https://doi.org/10.1111/cas.14846