Effect of Antiviral Prophylaxis Strategy for Chemotherapy-Associated Hepatitis B Reactivation in Non-Hodgkin's Lymphoma Patients with Hepatitis B Virus Infection: A Retrospective Cohort Study

Fan Yang · Huan-Ling Zhu · Chuan He ·
Jian-Jun Li · Bing Xiang · Xu Cui · Jie Huang ·
Jie Ji · Hong-Bing Ma · Ting Liu

Received: 25 March 2012 / Accepted: 31 August 2012 / Published online: 30 October 2012
© Indian Society of Haematology & Transfusion Medicine 2012

Abstract Recent data indicates that nucleoside/nucleotide analogue (NUC) is effective in preventing and controlling hepatitis B virus (HBV) reactivation in HBV-carrying cancer patients who undergo chemotherapy, but the ideal antiviral agent and optimal application protocol still needs to be determined. Meanwhile, it is uncertain whether those with past HBV infection require antiviral prophylaxis during chemotherapy. This report retrospectively analyzed non-Hodgkin's lymphoma (NHL) patients seen from January, 2004 to June, 2009 in West China Hospital. We found that the prevalence of chronic HBV infection in our NHL patients was 20.7 % while that of past HBV infection was 21.05 %. Compared with the high rate (25.6 %) of HBV reactivation in patients with chronic HBV infection, none of those with past HBV infection in fact had occult HBV infection thus none experienced reactivation. Of the 82 patients with chronic HBV infection who received chemotherapy, antiviral prophylaxis could significantly reduce the incidence of HBV reactivation (5.0 vs. 45.2 % in the control group) and the incidence of liver function damage (32.5 vs. 73.8 % in the control group). The results of the current study confirmed previous reports that prophylactic NUCs administration can effectively prevent HBV reactivation and significantly reduce the incidence of HBV reactivation especially for patients receiving rituximab-containing regimens. Due to the fact that none of individuals who had past HBV infection

developed HBV reactivation reported in our study, antiviral prophylaxis may not be required for patients with past HBV infection. Close observation of alanine aminotransferase and HBV-DNA contributes to early diagnosis and timely treatment of HBV reactivation.

Keywords HBV reactivation · Nucleoside/nucleotide analogue · Rituximab · Non-Hodgkin's lymphoma

Introduction

Hepatitis B is a major public health problem in the world. To the data of World Health Organization (WHO), it is estimated that about 2 billion people globally have been infected with the virus and approximately 350 million are chronically infected. Hepatitis B virus (HBV) is endemic in Asian countries. The prevalence of HBV infection, defined as the presence of hepatitis B surface antigen (HBsAg) in the blood, may be as high as 9.09 % among population aged over 3-year-old in China [1]. In addition, the presence of hepatitis B core antibody (HBcAb) is evidence of past HBV infection in individuals who are negative for HBsAg. Meanwhile, the epidemiology and incidence of patients with past HBV infection are uncertain. Moreover, occult HBV infection is used to describe the presence of HBV DNA without hepatitis B surface antigenemia. The prevalence of occult HBV is unclear and it is often observed in patients with HBcAb as the only HBV serological marker [2]. With a high rate of HBV carriers in non-Hodgkin's lymphoma (NHL) patients compared with the HBV carrier rate of the general population being frequently reported [3], HBV reactivation induced by anticancer agent has become a well-recognized complication both in HBV inactive carriers and individuals with progressive chronic HBV

F. Yang
West China School of Clinical Medicine, Sichuan University,
No. 37 Guoxue Alley, Chengdu, China

H.-L. Zhu (✉) · C. He · J.-J. Li · B. Xiang · X. Cui ·
J. Huang · J. Ji · H.-B. Ma · T. Liu
Department of Haematology, West China Hospital of Sichuan
University, No. 37 Guoxue Alley, Chengdu, China
e-mail: zhuhuanling@medmail.com.cn

infection. More importantly, it may result in varying degree of liver damage ranging from mild transient elevation of aminotransferase levels to fatal fulminant hepatic failure. It can even shorten survival prognosis. HBV reactivation may become a more common problem with the increasing incidence of NHL and the more widespread use of anti-cancer agent.

The nucleoside/nucleotide analogue (NUC) is a potent inhibitor of HBV replication, such as lamivudine, adefovir, and some new analogues (entecavir, telbivudine and tenofovir). It is an effective suppressor of HBV replication that reduces HBV–DNA in serum and improves liver injury in patients with hepatitis B. Several studies reported a beneficial effect of antiviral prophylaxis in the management of chemotherapy-induced HBV reactivation in patients with NHL who are positive for HBsAg [4–8]. However, the benefits of antiviral prophylaxis for the patients who had past HBV infection are unknown.

As immunotherapy such as rituximab is proved to be effective in the treatment of CD20-positive B cell lymphomas, it is increasingly incorporated into chemotherapy regimens. However, a study by Sera et al. [9] has shown that rituximab can affect the immunity against HBV, consequently increasing viral replication. In fact, there were several case reports of fulminant liver failure due to HBV reactivation in patients with either chronic HBV infection or past HBV infection (HBsAg negative, HBcAb positive) after treatment with rituximab, sometimes proving fatal [10–13]. The events leading to HBV reactivation during rituximab given alone or in combination with chemotherapy are presently being paid close attention.

Hence, in the current study, our aim was (1) to discuss the effect of prophylactic NUCs treatment and combined chemotherapy regimens which contain rituximab in HBV carriers or patients with past HBV infection who were receiving systemic treatment, and (2) to summarize the measures and efficacy for prevention and treatment in these kind of patients who encounter HBV reactivation or liver function damage during chemotherapy in our hospital.

Patients and Methods

Patients and Follow-up

The institutional review board approved this research project.

Data was collected from inpatient cases in hematology and oncology department of West China Hospital. We retrospectively analyzed 846 patients with NHL seen from January, 2004 to June, 2009. Four hundred ninety two patients were tested for HBsAg before treatment. Meanwhile, HBsAb and HBcAb test were both performed for

133 out of these patients. We altogether found 110 patients in accordance with key eligibility criteria as follows: newly diagnosed, histologically proven NHL and positive HBsAg and/or HBcAb; prechemotherapy liver function was basically normal, including alanine aminotransferase (ALT), total bilirubin (TB) and alkaline phosphatase (ALP) levels less than 1.25 times the upper limit of normal range (ULN)(normal ≤ 55 IU/L) and albumin(ALB) ≥ 30 g/L; pre-chemotherapy HBV DNA level was no more than 10^5 copies/mL. All participants were staged before treatment using the Ann Arbor staging system and received at least 2 cycles of systemic chemotherapy. Key exclusion criteria included: hepatocellular carcinoma or other primary liver diseases, such as hepatitis A, chronic hepatitis C, hepatitis D, or autoimmune hepatitis.

Participants were followed-up at least for 1 year from the date of diagnosis. Liver function tests, which included ALT, AST, ALP, GGT, LDH, ALB, GLB, TBIL, DBIL, had been performed prior to each cycle of chemotherapy being commenced and 1–2 months after completion of chemotherapy. The majority of patients had been tested for HBV DNA levels during the course of chemotherapy. According to whether NUCs and/or rituximab were used, patients with chronic HBV infection who was tested positive for HBsAg were divided into two group pairs. Prophylactic group patients started nucleoside analogue antiviral treatment before occurring liver function damage (an increase in ALT levels ≥ 2 -fold and HBV DNA levels ≥ 10 -fold compared with baseline levels) due to HBV reactivation. Rituximab group patients got at least four courses treatment of rituximab alone or in combination with chemotherapy. All the HBV DNA quantification tests were performed by the clinical laboratory of West China Hospital.

Definitions

The severity of hepatitis was defined according to WHO criteria. Grade I was defined as an elevation in the ALT or TB level $>(1.25–2.5) \times \text{ULN}$; Grade II was defined as an elevation $>(2.5–5.0) \times \text{ULN}$; Grade III was defined as an elevation $>(5.0–10.0) \times \text{ULN}$; and Grade IV was defined as an elevation $>10.0 \times \text{ULN}$.

Hepatitis that was attributable to HBV reactivation was defined as an increase in HBV DNA levels ≥ 10 -fold compared with baseline levels or an absolute increase $>10^5$ copies/mL in the HBV DNA level in the absence of other systemic infection. For the purpose of this study and based on a definition described by Yeo et al., HBV reactivation was defined as an increase in HBV DNA levels ≥ 10 -fold compared with baseline levels accompanied with liver function damage during the course of chemotherapy or after the completion of chemotherapy.

Disruption of chemotherapy was defined as either a premature termination of chemotherapy or a delay more than 8 days of chemotherapy between cycles.

Statistical Analysis

Patient background characteristics included age, gender, stage, and immunopathology. Two groups were compared by using Chi-square tests or Fisher's exact tests, which also were used to compare the incidence of HBV reactivation and liver function damage between the groups. Two-tailed *P* values of ≤ 0.05 were regarded as significant. The statistical analyses were done using the SPSS13.0 software.

Results

Patients' Characteristics

Figure 1 summarized the hepatitis B profile of the NHL patients in current study. Among the 492 patients tested for HBsAg, the prevalence of chronic HBV infection was 20.7 % (102 of 492). Importantly, all of these 102 patients had a HBV DNA test performed, which was positive in 26 patients. The pre-chemotherapy HBV DNA level was less than 10^5 copies/mL in 15 patients while other 11 patients' HBV DNA level was over 10^5 copies/mL.

Of the 133 patients who received both HBsAg and HBcAb tests, 28 (21.05 %) tested positive for HBcAb only. And 25 of these 28 patients had a HBV DNA test performed, which was negative in all these patients. All of the 28 patients with past HBV infection received chemotherapy without having antiviral prophylaxis when informed consent was obtained; there were 5 females and 23 males.

Median age of these patients was 54.5 years (range: 21–77), and there were 19 patients who were accepted for classic CHOP chemotherapy and 9 patients with B cell types were treated with a regimen including rituximab.

Table 1 summarized the baseline characteristics of the 82 patients with chronic HBV infection who received chemotherapy. Median age of these patients was 47 years (range: 12–78). They received a median of 7 cycles of chemotherapy (range: 2–15). As shown, there was no significant difference between prophylactic and control group with regard to gender distribution, age, stage, immunopathology and HBeAg status. However, patients in the rituximab group appeared more likely to be given prophylactic antiviral treatment (19 vs. 9; *P* = 0.013) and have B cell types (28 vs. 0; *P* = 0.038).

Clinical Outcomes of Patients Developing

All of the 28 patients who had past HBV infection underwent systemic treatment, including 9 receiving rituximab. It is interesting to note that none of the patients with past HBV infection received antiviral prophylaxis, compared with 48.78 % of the patients with chronic HBV infection. Furthermore, we noted that none of the 28 patients experienced HBV reactivation.

Among the 102 patients with chronic HBV infection at the time of diagnosis, 13 refused to receive systemic treatment and 7 patients whose HBV DNA level was over 10^5 copies/mL had no chemotherapy but received NUC administration more than 1 month. Of the 40 patients with chronic HBV infection in the prophylactic group, the median number of chemotherapy cycles was 8 (range: 2–15 cycles). The choice of the antiviral agents included: 2 of the 40 patients with adefovir (at a dose of 10 mg daily), 1

Fig. 1 Hepatitis B profile of non-Hodgkin's lymphoma patients is shown. HBsAg indicates hepatitis B virus (HBV) surface antigen; HBcAb, antibody to hepatitis B core antigen; -ve, negative; +ve, positive

Table 1 General information with chronic HBV infection between prophylactic and control group, rituximab and non-rituximab group

Characteristic	Prophylactic group No. (%)	Control group No. (%)	<i>P</i> value	Rituximab group No. (%)	Non-rituximab group No. (%)	<i>P</i> value
Total no. pt.	40	42		28	54	
Gender						
Male	32 (80)	28 (66.7)	.173	22 (78.6)	38 (70.4)	0.427
Female	8 (20)	14 (33.3)		6 (21.4)	16 (29.6)	
Age (y)						
Median (range)	44.5 (20–73)	51 (12–78)	.519 ^a	46 (32–73)	49 (12–78)	0.922 ^a
Ann Arbor Staging						
I–II	11 (27.5)	6 (14.3)	.140	7 (25)	10 (18.5)	0.492
III–IV	29 (72.5)	36 (85.7)		21 (75)	44 (88.5)	
Immunopathology						
B cell types	37(92.5)	35 (83.3)	.352	28 (100.0)	44 (88.5)	0.038
T cell types	3 (7.5)	7 (16.7)		0 (0)	10 (18.5)	
HBeAg status						
Negative	36 (90.0)	40 (95.2)	.427 ^b	27 (96.4)	49 (90.7)	0.659 ^b
Positive	4 (10.0)	2 (4.8)		1 (3.6)	5 (9.3)	

^a Wilcoxon two-simple (two-sided) test^b Fisher's exact (two-sided) test

patient with entecavir (at a dose of 0.5 mg daily), 1 patient with telbivudine (at a dose of 600 mg daily), and other 36 of the 40 patients with lamivudine (at a dose of 100 mg daily). Liver function damage occurred in 13 patients; 2 episodes were attributed to HBV reactivation. According to WHO acute toxicity assessment criteria, the severity of hepatitis was Grade I in 7 patients, Grade II in 4 patients, and Grade IV in 2 patients. The antiviral agents were tolerated well and were not associated with any unexpected or additional toxicity from chemotherapy. By contrast, of the 42 patients in the control group, the median number of chemotherapy cycles was 6 (range: 2–15 cycles). Thirty one patients developed liver function damage; the severity

of hepatitis was Grade I in 14 patients, Grade II in 9 patients, Grade III in 3 patients, and Grade IV in 5 patients. A total of 19 patients developed HBV reactivation and 18 of these episodes presented abnormal liver function. One case worthy to be pointed out was that the patient was died of serious infection without liver function damage when the HBV DNA elevation was detected after the completion of chemotherapy.

Tables 2 and 3 compared the HBV DNA reactivation and chemotherapy-associated hepatitis between the prophylactic and control groups respectively. In the prophylactic group, there was significantly less incidence of HBV reactivation (5.0 vs. 45.2 % in the control group; $P = 0.000$),

Table 2 Comparison of HBV reactivation of patients between prophylactic and control group

Time	No. of patients	Prophylactic group ^a			No. of patients	Control group ^a			<i>P</i> value
		Yes	No	%		Yes	No	%	
Prechemotherapy	40	0	40	0	42	0	42	0	
2 Cycles	40	1	39	2.5	42	3	39	7.1	0.644
4 Cycles	37	2	35	5.4	37	10	27	27.0	0.012
6 Cycles	27	1	26	3.7	27	7	20	25.9	0.050 ^b
8 Cycles	22	1	21	4.5	14	8	6	57.1	0.001 ^b
Total	40	2	38	5.0	42	19	23	45.2	0.000

^a Yes, No. of pt. with HBV reactivation; No, No. of pt. without HBV reactivation; %, Reactivation %^b Fisher's exact (two-sided) test

Table 3 Comparison of chemotherapy-associated hepatitis of patients between prophylactic and control group

	Prophylactic group, <i>n</i> = 40		Control group, <i>n</i> = 42		<i>P</i> value
	No. of patients	%	No. of patients	%	
Incidence of HBV reactivation	2	5.0	19	45.2	0.000
Liver function damage	13	32.5	31	73.8	0.000
Due to HBV reactivation	2	–	18	–	
Due to others	11	–	13	–	
Disruption in chemotherapy	4	10.0	13	31.0	0.019
Due to HBV reactivation	2	–	13	–	
Due to others	2	–	0	–	
Mortality	3	7.5	10	23.8	0.043
Due to hepatitis	2	–	3	–	
Due to tumor progression	1	–	2	–	
Due to infection	0	–	4	–	
Due to others	0	–	1	–	

less severity of hepatitis (32.5 vs. 73.8 % in the control group), fewer interval delays (10.0 vs. 31.0 % in the control group). The incidence of the presence of serum HBV DNA was elevated with longer chemotherapy. After the chemotherapy of 2,4,6,8 cycles, the incidences of the presence of serum HBV DNA were 4.9 % (4/82), 16.2 % (12/74), 14.8 % (8/54), and 25 % (9/36), respectively.

Table 4 compared the rate of HBV DNA reactivation of patients receiving rituximab and non-rituximab. No significant difference was detected [21.4 % (95 %CI, 8–41 %) versus 27.8 % (95 %CI, 15.8–39.7 %)]. In the rituximab group, the median number of chemotherapy cycles was 6.5 (range: 2–15 cycles). Liver function damage

occurred in 11 patients including Grade I in 7 patients, Grade II in 2 patients, and Grade IV in 2 patients. By contrast, the median number of chemotherapy cycles in the non-rituximab group was 7 (range: 2–15 cycles). Thirty three patients presented abnormal liver function; the severity of hepatitis was Grade I in 14 patients, Grade II in 11 patients, Grade III in 3 patients, and Grade IV in 5 patients. The occurrence rate of liver function damage was similar between the two groups.

Of the 28 patients with chronic HBV infection who having rituximab-based treatment, 6 patients experienced reactivation and all of them did not receive antiviral prophylaxis. The incidence of HBV reactivation in those without prophylactic NUC treatment was significantly higher than those who received antiviral prophylaxis (66.7 vs. 0.0 %; *P* = 0.000). Patients who got prophylactic NUC treatment had a significantly lower risk of liver function damage (21.1 vs. 77.8 %; *P* = 0.010).

HBV reactivation occurred in 21 participants in the current study. NUCs antiviral treatment (lamivudine 100 mg once daily) was initiated after diagnosis of HBV reactivation in 11 patients. Nine patients had marked decline in HBV DNA levels following initiation of lamivudine therapy. For a median of 2 months (range: 0.5–6 months) later, the serum HBV DNA was undetectable. Only one patient's regimen was then changed to adefovir due to treatment failure with lamivudine, by the way, the tyrosine-methionine-aspartate-aspartate (YMDD) motif mutation was detected. The patient steadily improved and his serum HBV DNA was undetectable later. Remaining one patient developed fulminant hepatic failure and died. Supportive therapy without antiviral treatment was given in other 10 patients. Only one out of the ten patients who was simultaneously diagnosed with herpes simplex virus (HSV) infection received acyclovir; 3 months later, his serum HBV DNA was undetectable. However, HBV DNA was still detectable in remaining 9 patients. During the course of antiviral treatment, NUCs were safe, free from toxicity, and could be well-tolerated.

Table 4 Comparison of hbv reactivation of patients between the rituximab group and the non-rituximab group

Time	No. of patients	Rituximab group ^a			No. of patients	Non-rituximab group ^a			<i>P</i> value
		Yes	No	%		Yes	No	%	
Prechemotherapy	28	0	28	0	54	0	54	0	
2 Cycles	28	1	27	3.6	54	3	51	5.6	1.000
4 Cycles	25	3	22	12.0	49	9	40	18.4	0.712
6 Cycles	20	4	16	20.0	34	4	30	11.8	0.670
8 Cycles	12	3	9	25.0	24	6	18	25.0	1.000 ^b
Total	28	6	22	21.4	54	15	39	27.8	0.532

^a Yes, No. of pt. with HBV reactivation; No, No. of pt. without HBV reactivation; % Reactivation %

^b Fisher's exact (two-sided) test

Discussion

The prevalence of chronic HBV infection in our NHL patients was 20.7 %, while that of past HBV infection was 21.05 %. As compared to a study by Targhetta et al. [14] involving 1,087 NHL patients, among whom 36 % were found to be isolated HBcAb positive, the prevalence of past HBV infection is relatively low in present study. Moreover, none of them in fact had occult HBV infection, defined as a detectable HBV DNA level. This finding may be in contrast to a recent study including 58 patients testing positive for HBcAb only and having a HBV DNA test performed, of whom 5.2 % found to have occult HBV infection [15]. Because of the small sample size, we also suggest that patients with isolated HBcAb positive still need to test HBV DNA levels for the screening of HBV infection. Some patients with HBV viremia who have not been detected are also at risk of HBV reactivation.

The high rate (25.6 %) of HBV reactivation in patients with chronic HBV infection was consistent with previous reports which suggested the incidence of HBV reactivation in the population of HBsAg positive lymphoma during chemotherapy was 20–55 % [16]. Two possible mechanisms may be involved in HBV reactivation. Immunosuppression due to chemotherapy may enhance HBV replication and thereby result in direct toxicity of hepatocytes. On the other hand, the administration of cytotoxic/immunosuppressive agents may allow widespread infection of hepatocytes. Then, hepatocyte destruction could appear while immune response recovers after withdrawal of chemotherapy [17]. Because of study limitations and unavailability of data, we could not analyze some important questions. Previous studies suggested that ALT elevation that occurred in chemotherapy-induced HBV reactivation was usually preceded by HBV DNA elevation for 2–3 weeks [18, 19]. Some worth to be noticed in the current study was that HBV DNA surge was tested after 1 month of the ALT elevation in 2 patients. This lack of timely monitoring of the parameters may reflect the results. For chemotherapy-associated hepatitis, monitoring of HBV DNA level is now the gold standard for diagnosis of HBV reactivation. Therefore, patients without NUC prophylaxis should be monitored weekly or biweekly by HBV DNA quantification during the course of chemotherapy so that antiviral therapies could be given in time [18].

To the best of our knowledge, prophylactic use of an effective NUC can be an attractive way to prevent hepatitis during chemotherapy. A number of reports indicated that antiviral prophylaxis could significantly reduce the incidence and severity of hepatitis in HBV carriers who receive chemotherapy [4, 5, 8, 20]. Our study confirmed the efficacy of NUCs in preventing chemotherapy-associated HBV reactivation in NHL patients during chemotherapy.

No hepatic enzyme flares or reduction in chemotherapy dosage were observed in those receiving this agent. Also, as reported by other investigators, the adverse effect profile of NUCs does not overlap with that of chemotherapeutic agents making this agent particularly suitable for simultaneous use with chemotherapy and having a good safety record [6, 7, 21]. Despite the benefits of prophylactic NUCs approach, the administrations of NUCs prophylaxis in patients with chronic HBV infection were less than half in our study. And for the majority of patients, lamivudine is selected and used. For the reason that relatively low cost of antiviral medications and high cost of managing patients with hepatitis flares or hepatic failure, it should be used widely in developing countries. Nevertheless, it is well-known that long-term lamivudine therapy is limited by the appearance of antiviral resistance [22]. Thus, some newer agents with the optimal resistance profile, i.e. entecavir or tenofovir, as first-line monotherapies especially in patients those with a high HBV DNA level who need for long-term (more than 12 months) NUC administration have been recommended in 2009 and 2012 guidelines published by EASL [23, 24].

The results of the present study found the risk of reactivation during the course of systemic chemotherapy to be low in patients with past HBV infection; none of the 28 patients experienced reactivation. But it is of note that accumulating evidence shows that patients with past HBV infection are still at risk for reactivation after use of anti-cancer agents, especially given rituximab, and may be considered for prophylaxis [12, 13, 25]. Although this issue was not explicitly expounded in our manuscript due to the small case number, it may be considered as an important issue in future studies. We suggest the routine use of antiviral prophylaxis in this group of patients might not be required for the low risk of reactivation and high cost of antiviral medications.

We observed that although most patients continued antiviral agents for 1–3 months after completion of chemotherapy, HBV reactivation after withdrawal from antiviral agents was still found. American Association for the Study of Liver Diseases recommended that the prophylaxis should be initiated 2–3 weeks before chemotherapy and maintained for 6–12 months after cessation of therapy, based on level III evidence. More importantly, in those with a high baseline viral load >2,000 IU/mL before chemotherapy need to continue antiviral treatment until therapeutic end points for chronic hepatitis B are reached. Meanwhile, some indicated that the efficacy of therapeutic use of antiviral agents may depend on an early start of treatment [4, 18].

We caution that no significant difference was detected in the rate of reactivation between patients receiving rituximab-containing or non-containing regimens. But it is also

interesting to note that a larger proportion in patients having rituximab-containing regimens received routine antiviral prophylaxis, and that likely contributed to the result. Since the initial use of rituximab in the clinic, a number of cases of HBV reactivation after rituximab administration have been reported previously [26, 27]. Moreover, it has been suggested that rituximab may augment the risk of reactivation compared to chemotherapy alone [12, 28, 29]. We found that none of whom having rituximab-based treatment and then experienced reactivation received antiviral prophylaxis. A 44-year-old male who was treated with combination chemotherapy of rituximab plus CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) displayed fatal fulminant hepatitis B after 3 cycles of chemotherapy. We suggest that the states of HBV infection should be monitored closely even though one shows to be negative for HBV DNA levels and prophylaxis should be considered for patients who are scheduled to receive rituximab. Prophylactic or pre-emptive use of antiviral agents and close monitoring of HBV-related markers including HBV DNA should be considered for high-risk (either HBsAg-positive or anti-HBcAb-positive) patients scheduled to receive rituximab-containing treatment.

Until recently, for this issue, data on patients with other malignancies has been limited. Although the prevalence has been noted to be lower in other cancers, patients with other malignancies who receive immunosuppressive or chemotherapy should be screened for HBV status prior to chemotherapy. Cancer patients found to be HBV carriers or had occult HBV infection should be given NUC prophylaxis as well as lymphoma patients, with the similar therapeutic scheme.

In conclusion, all patients diagnosed with NHL should be screened for HBV status (including HBsAg, HBsAb, HBcAb, HBeAg and HBeAb) prior to the administration of chemotherapy. When any one of the result is positive, the patient should also be tested for the presence of HBV DNA because it remains uncertain whether patients with detectable HBV DNA in this setting are at a risk of reactivation. Even though all markers are negative, vaccination against HBV in such seronegative patients is highly recommended. Furthermore, HBsAg-positive candidates for chemotherapy, regardless of the level of the viral load, should receive pre-emptive NUC administration during therapy and then for 12 months after cessation of therapy. Use of NUCs as prophylaxis in HBV or occult HBV carriers has become a standard strategy, but for those with an undetectable HBV DNA level but positive for HBcAb, the benefits of prophylactic NUCs administration still seem to be in dispute. These patients should be followed carefully through ALT and HBV DNA tests so as to treat with NUC in time. Further prospective studies are certainly needed to

clarify the cost-effectiveness of antiviral prophylaxis in this group of patients.

Acknowledgments We thank Dr. Jin Liu in the gathering of clinical data for this study and all Faculties of the Department of Hematology, West China Hospital of Sichuan University, for their kind assistance.

References

1. Liang XF, Chen YS, Wang XJ, He X, Chen LJ, Wang J, Lin CY, Bai HQ, Yan J, Cui G, Yu JJ (2005) A study on the sero-epidemiology of hepatitis B in Chinese population aged over 3-years old. *Zhonghua Liu Xing Bing Xue Za Zhi* 26(9):655–658
2. Schmeltzer P, Sherman KE (2010) Occult hepatitis B: clinical implications and treatment decisions. *Dig Dis Sci* 55(12):3328–3335. doi:10.1007/s10620-010-1413-0
3. Qin XT, Lu Y, Chen XQ, Xu HP, Fan HJ (2007) Correlation of hepatitis B virus infection to non-Hodgkin's lymphoma. *Ai Zheng* 26(3):294–297. doi:1000-467X200703294
4. Li YH, He YF, Jiang WQ, Wang FH, Lin XB, Zhang L, Xia ZJ, Sun XF, Huang HQ, Lin TY, He YJ, Guan ZZ (2006) Lamivudine prophylaxis reduces the incidence and severity of hepatitis in hepatitis B virus carriers who receive chemotherapy for lymphoma. *Cancer* 106(6):1320–1325. doi:10.1002/cncr.21701
5. Liao CA, Lee CM, Wu HC, Wang MC, Lu SN, Eng HL (2002) Lamivudine for the treatment of hepatitis B virus reactivation following chemotherapy for non-Hodgkin's lymphoma. *Br J Haematol* 116(1):166–169
6. Rossi G (2003) Prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with hemato-oncological neoplasias treated with chemotherapy. *Leuk Lymphoma* 44(5):759–766. doi:10.1080/104281903100006351
7. Rossi G, Pelizzari A, Motta M, Puoti M (2001) Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. *Br J Haematol* 115(1):58–62
8. Yeo W, Chan PK, Ho WM, Zee B, Lam KC, Lei KI, Chan AT, Mok TS, Lee JJ, Leung TW, Zhong S, Johnson PJ (2004) Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 22(5):927–934. doi:10.1200/JCO.2004.05.161
9. Sera T, Hiasa Y, Michitaka K, Konishi I, Matsuura K, Tokumoto Y, Matsuura B, Kajiura T, Masumoto T, Horiike N, Onji M (2006) Anti-HBs-positive liver failure due to hepatitis B virus reactivation induced by rituximab. *Intern Med* 45(11):721–724
10. Dervite I, Hober D, Morel P (2001) Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 344(1):68–69. doi:10.1056/NEJM200101043440120
11. Domingo-Domenech E, Gonzalez-Barca E, Estany C, Sureda A, Besalduch J, Fernandez de Sevilla A (2002) Combined treatment with anti-CD20 (rituximab) and CHOP in relapsed advanced-stage follicular lymphomas. *Haematologica* 87(11):1229–1230
12. Law JK, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida EM (2005) Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. *Leuk Lymphoma* 46(7):1085–1089. doi:10.1080/10428190500062932
13. Sarrecchia C, Cappelli A, Aiello P (2005) HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. *J Infect Chemother* 11(4):189–191. doi:10.1007/s10156-005-0385-z

14. Targhetta C, Cabras MG, Mamusa AM, Mascia G, Angelucci E (2008) Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy. *Haematologica* 93(6):951–952. doi:[10.3324/haematol.12557](https://doi.org/10.3324/haematol.12557)
15. Koo YX, Tan DS, Tan IB, Tao M, Chow WC, Lim ST (2010) Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. *Cancer* 116(1):115–121. doi:[10.1002/cncr.24742](https://doi.org/10.1002/cncr.24742)
16. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ (2000) Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 62(3):299–307. doi:[10.1002/1096-9071](https://doi.org/10.1002/1096-9071)
17. Liang R, Lau GK, Kwong YL (1999) Chemotherapy and bone marrow transplantation for cancer patients who are also chronic hepatitis B carriers: a review of the problem. *J Clin Oncol* 17(1):394–398
18. Kohrt HE, Ouyang DL, Keeffe EB (2006) Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 24(7):1003–1016. doi:[10.1111/j.1365-2036.2006.03081.x](https://doi.org/10.1111/j.1365-2036.2006.03081.x)
19. Yeo W, Johnson PJ (2006) Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 43(2):209–220. doi:[10.1002/hep.21051](https://doi.org/10.1002/hep.21051)
20. Dai MS, Wu PF, Lu JJ, Shyu RY, Chao TY (2004) Preemptive use of lamivudine in breast cancer patients carrying hepatitis B virus undergoing cytotoxic chemotherapy: a longitudinal study. *Support Care Cancer* 12(3):191–196. doi:[10.1007/s00520-003-0549-2](https://doi.org/10.1007/s00520-003-0549-2)
21. Shibolet O, Ilan Y, Gillis S, Hubert A, Shouval D, Safadi R (2002) Lamivudine therapy for prevention of immunosuppressive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. *Blood* 100(2):391–396
22. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS (2007) Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 45(4):1056–1075. doi:[10.1002/hep.21627](https://doi.org/10.1002/hep.21627)
23. European Association for the Study of the Liver (2009) EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 50(2):227–242. doi:[10.1016/j.jhep.2008.10.001](https://doi.org/10.1016/j.jhep.2008.10.001)
24. European Association for the Study of the Liver (2012) EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 57(1):167–185. doi:[10.1016/j.jhep.2012.02.010](https://doi.org/10.1016/j.jhep.2012.02.010)
25. Fukushima N, Mizuta T, Tanaka M, Yokoo M, Ide M, Hisatomi T, Kuwahara N, Tomimasu R, Tsuneyoshi N, Funai N, Sueoka E (2009) Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. *Ann Oncol* 20(12):2013–2017. doi:[10.1093/annonc/mdp230](https://doi.org/10.1093/annonc/mdp230)
26. Tsutsumi Y, Shigematsu A, Hashino S, Tanaka J, Chiba K, Masauzi N, Kobayashi H, Kurosawa M, Iwasaki H, Morioka M, Asaka M, Imamura M (2009) Analysis of reactivation of hepatitis B virus in the treatment of B cell non-Hodgkin's lymphoma in Hokkaido. *Ann Hematol* 88(4):375–377. doi:[10.1007/s00277-008-0585-6](https://doi.org/10.1007/s00277-008-0585-6)
27. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, Chan HL, Hui EP, Lei KI, Mok TS, Chan PK (2009) Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 27(4):605–611. doi:[10.1200/JCO.2008.18.0182](https://doi.org/10.1200/JCO.2008.18.0182)
28. Dai MS, Chao TY, Kao WY, Shyu RY, Liu TM (2004) Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. *Ann Hematol* 83(12):769–774. doi:[10.1007/s00277-004-0899-y](https://doi.org/10.1007/s00277-004-0899-y)
29. Tsutsumi Y, Kanamori H, Mori A, Tanaka J, Asaka M, Imamura M, Masauzi N (2005) Reactivation of hepatitis B virus with rituximab. *Expert Opin Drug Saf* 4(3):599–608. doi:[10.1517/14740338.4.3.599](https://doi.org/10.1517/14740338.4.3.599)