

# Real-World Experience of Telbivudine and Lamivudine as Antiviral Prophylaxis for Chemotherapy-Related Hepatitis B Reactivation

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## ABSTRACT

**Background:** There is currently no data regarding the efficacy of prophylactic telbivudine in hepatitis B patients undergoing chemotherapy. This study aims to describe the results of pre-emptive telbivudine and lamivudine to prevent chemotherapy-related HBV reactivation.

**Methods:** The medical records of all patients with HBsAg positive or HBs-Ag negative, anti-HBc positive, who were referred to the hepatology clinic between May 2014 and December 2016, were retrospectively reviewed. As this is a descriptive study, no statistical analysis was done.

**Results:** A total of 52 patients with prophylactic telbivudine or lamivudine therapy were included, with 26 patients in each group. Rituximab-based treatment was given in nine and five patients in the telbivudine and lamivudine group, respectively. The number of patients who completed antiviral treatment up to six months after chemotherapy was 17 patients in each group. There was less incidence of HBV reactivation in the telbivudine group (2 of 17 patients, 11.8%) than in the lamivudine group (7 of 17 patients, 41.2%). Delayed reactivation was noticed in 1 of 2 patients in the telbivudine group and 3 of 7 patients in the lamivudine group. The median log<sub>10</sub>[HBV DNA] at reactivation was 4.52 (1.70 – 8.35) IU/mL. Severe hepatitis was observed in two patients in the lamivudine group and one patient in the telbivudine group. Of 34 patients who completed antiviral treatment, two patients died due to primary cancer. No interruption of chemotherapy or mortality due to hepatitis was noticed in both groups.

**Conclusions:** Preemptive telbivudine or lamivudine in HBsAg positive or HBsAg negative, anti-HBc positive patients seems to be a good treatment option.

## INTRODUCTION

Hepatitis B reactivation in patients undergoing chemotherapy is associated with substantial morbidity and mortality. This potentially fatal condition may occur during and after therapy in patients with chronic hepatitis B. There is also a risk of hepatitis B reactivation in patients with a history of hepatitis B exposure, especially those who are treated with B-cell depleting agents, such as, rituximab. Their laboratory results show negative hepatitis B surface antigen (HBsAg) and positive antibody to hepatitis B core antigen (anti-HBc) [1,2]. Reactivation of hepatitis B may interrupt the chemotherapy cycle, delay treatment of the underlying disease, and finally increase patients' morbidity or mortality.

Chemotherapy results in depletion of B and T lymphocytes, as well as NK cells at two weeks after

chemotherapy. Although their levels recovered to some extent, B and CD4+ T cells remained significantly depleted at 9 months post-chemotherapy [3]. Lazdina et al. [4] reported that specific cytotoxic T cells (CTLs) response to exogenous HBcAg particles is B cell-dependent. Although the mechanism of chemotherapy-associated HBV reactivation needs further studies, it is suggested that suppression of lymphocytes results in the reduction of cytokine production that inhibits hepatitis B viral replication [5].

An increase in viral replication is characterized by the increase of HBV DNA, together with the reappearance of hepatitis B e antigen (HBeAg) and HBsAg. Interruption of chemotherapy will be followed by immune restoration, in which immune cells may recognize hepatocytes infected with hepatitis B virus and destroy them. At this stage, an increase in ALT and bilirubin levels may

appear and lead to clinical features of acute hepatitis or hepatic decompensation (jaundice and coagulopathy) or hepatic failure. Some patients will enter the recovery phase, during which the ALT level decreases and HBV DNA returns to baseline [6–8].

To prevent hepatitis B reactivation, it is recommended that all cancer patients who are planned for chemotherapy, be screened for the presence of HBsAg and anti-HBc [9–11]. Patients with positive HBsAg or anti-HBc should receive prophylactic antiviral treatment, according to their HBV DNA and chemotherapy regimen to prevent reactivation [10,12]. Prophylaxis with lamivudine is associated with a lower risk of HBV reactivation, compared with no prophylaxis [13]. Nevertheless, lamivudine is known for its low genetic barrier to resistance and high mutation rate [14]. Meanwhile, antiviral with a high genetic barrier to resistance, entecavir, and tenofovir, was costly and not readily available in most hospitals in Indonesia. Telbivudine is a nucleoside analog that shares a drug resistance profile with lamivudine [15], but with greater HBV DNA suppression and less resistance in both the HBeAg-negative and the HBeAg-positive groups [16]. Currently, there is no data regarding the efficacy of prophylactic telbivudine therapy in patients undergoing chemotherapy. This study aims to describe the result of preemptive telbivudine and lamivudine to prevent chemotherapy-related HBV reactivation among patients with different types of malignancy.

## METHODS

### Study design

A descriptive study was conducted in “Dharmais” Hospital, Indonesian National Cancer Center, to evaluate all cancer patients with positive HBsAg or anti-HBc, receiving prophylactic antiviral treatment between May 2014 and December 2016. Before starting chemotherapy, all patients were screened for hepatitis B by their treating oncologists. If their HBsAg or anti-HBc were positive, they were referred to the hepatology clinic for further treatment. Medical records of the patients treated with prophylactic antiviral therapy were retrospectively reviewed. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of “Dharmais” Hospital, Indonesian National Cancer Center (ethical clearance letter’s reference number: KEPK/029/VII/2015).

### Patients

Between May 2014 and December 2016, we enrolled cancer patients aged 18 years or older who were treated with chemotherapy and had positive serum HBsAg and/

or positive anti-HBc. They received either 600 mg of telbivudine or 100 mg of lamivudine once daily as prophylactic therapy. Patients’ baseline ALT level should be less than 2x of the upper limit of normal and bilirubin level should be less than 2 mg/dL. Patients with previous treatment with any anti-HBV nucleoside/nucleotide analog or interferon, baseline estimated glomerular filtration rates (eGFR)  $\leq$  30 ml/min, discontinuation of lamivudine or telbivudine during chemotherapy, histories of other primary liver diseases, such as chronic hepatitis C, alcoholic liver diseases, and autoimmune hepatitis, were excluded from this study.

### Treatment

Prophylactic therapy was initiated within one week before the first course of chemotherapy and was maintained for at least six months after the cessation of chemotherapy. This treatment duration was based on the recommendation of the 2009 guidelines of the American Association for the Study of Liver Diseases (AASLD) [17]. The decision of the treatment choice with telbivudine or lamivudine was made by treating physicians. During the study period, there were only telbivudine and lamivudine that were readily available in our hospital while other nucleosides/tide analogs, i.e., tenofovir and entecavir, were not available.

### Assessment

Patients were followed up each month during their chemotherapy cycles, which varied depending on their primary cancer and duration of chemotherapy regimen, up to six months after cessation of chemotherapy. Patients were assessed for the clinical condition at 1-month intervals and ALT, bilirubin, and creatinine at 3-month intervals during and after discontinuation of prophylactic antiviral therapy. HBV DNA assay was conducted at 3- to 6-month intervals or when reactivation was suspected. Baseline serum HBsAg and anti-HBc were assessed at “Dharmais” Hospital laboratory.

HBsAg and anti-HBc were measured using the Abbott ARCHITECT i2000SR (Abbott Diagnostic, Indonesia). HBV DNA was analyzed using the COBAS Taqman HBV Test (Roche, Indonesia) under manufacturer instructions. Serological results were considered reactive if HBsAg and anti-HBc titers were above 0.05 IU/mL and 1.0 IU/mL, respectively. The limit of quantification of HBV DNA was 10 IU/mL.

### Definitions and outcome measures

Patients were classified as having high and low HBV DNA levels based on the cut-off level of 2000 IU/mL [18]. If there was an increase of HBV DNA level of 10-fold or more compared with previous levels, patients were categorized as having HBV reactivation [19].

Patients with HBV reactivation detected after discontinuation of antivirals were categorized as having delayed HBV reactivation [20]. Elevation of ALT level was classified as “mild” (ALT < 80 U/L), “moderate” (80 – 200 U/L), and “severe” (> 200 U/L). Interruption of chemotherapy was described as a delay of chemotherapy treatment schedules of more than seven days or early discontinuation of chemotherapy.

The primary endpoints of this study were the number of HBV reactivations and hepatitis during and after the treatment with lamivudine and telbivudine. The secondary endpoints were the interruption of chemotherapy and mortality.

### Statistical analysis

No statistical analysis was done for this descriptive study. The data were presented as number (%) or median (range) as appropriate.

## RESULT

### Patient demographics and baseline characteristics

Between May 2014 and December 2016, there were 69 HBsAg and or anti-HBc seropositive patients with various types of malignancy, who were referred to our clinic for prophylaxis. Seventeen patients were excluded due to various reasons (**Figure 1**) and a total of 52 patients were included. The choice of antiviral treatment was based on the decision of treating physicians. There were 26 patients in each group. The demographic and laboratory baseline characteristics are depicted in **Table 1**. Rituximab-based treatment was given in nine and five patients in the telbivudine and lamivudine groups, respectively. We did not compare the baseline demographic data due to our small number of patients.

### The outcome of antivirals prophylaxis

Completion of prophylactic antiviral treatment at six months after chemotherapy was achieved in 16 and 17 patients in telbivudine and lamivudine groups, respectively. A total of 9 patients experienced HBV reactivation. Less incidence of HBV reactivation was observed in the telbivudine group (2 of 17 patients, 11.8%) than in the lamivudine group (7 of 17 patients, 41.2%). Delayed reactivation was noticed in 1 of 2 patients in the telbivudine group and 3 of 7 patients in the lamivudine group (**Figure 1**). The median log<sub>10</sub>[HBV DNA] at reactivation was 4.52 (1.70 – 8.35) IU/mL. One of 9 patients with HBV reactivation had negative HBsAg and positive anti-HBc status (**Table 2**). This patient was given a rituximab-based chemotherapy regimen. Severe hepatitis was observed in two patients

in the lamivudine group and one patient in the telbivudine group (**Table 2**).

Five patients with reactivation were given salvage tenofovir disoproxil fumarate (TDF) 300 mg daily (**Table 2**). Of 34 patients who completed antiviral treatment, two patients died due to primary cancer. No disruption of chemotherapy or mortality due to hepatitis was noticed in both groups. Estimation of the risk factors of HBV reactivation could not be conducted due to the small number of patients, which might result in low statistical power.

## DISCUSSION

Reactivation of hepatitis B during immunosuppressive therapy may vary clinically from asymptomatic to acute liver failure and death. Thus, routine HBV screening is recommended among all patients who are planned to undergo immunosuppressive therapy, such as B-cell depleting agents, systemic chemotherapy, high-dose corticosteroid, etc. Prophylactic therapy with oral anti-HBV therapies is strongly recommended for patients with a high or medium risk of reactivation [10]. The risk of reactivation is categorized as high, medium, or low, according to the type of immunosuppressive therapies and HBsAg-positive status of the patient. The anticipated incidence of HBV reactivation without antiviral prophylaxis in high-, medium-, and low-risk is > 10%, 1–10%, and < 1%, respectively [21].

Lamivudine was the most extensively studied antiviral in the setting of HBV reactivation prophylaxis, whereas there is currently minimal data regarding telbivudine in this setting. Lamivudine and telbivudine are categorized as antiviral with a low barrier of resistance [22,23]. A phase III clinical trial found that viral resistance was observed in 25.1% and 39.5% of hepatitis B e antigen (HBeAg)-positive patients and in 10.8% and 25.9% of HBeAg-negative patients after 2 years of telbivudine and lamivudine therapy, respectively [24]. Thus, entecavir or tenofovir is currently recommended by the European Association for the Study of the Liver (EASL) and American Gastroenterological Association (AGA) as a prophylactic treatment for HBsAg-positive patients receiving chemotherapy [10,12]. However, lamivudine or telbivudine may be selected if the anticipated treatment duration is short (≤ 12 months) and baseline serum HBV DNA is not detectable [17]. Telbivudine has been shown to have more potent HBV DNA suppression than lamivudine [22] and was found to improve renal function in patients with compensated and decompensated cirrhosis, especially among patients with an increased risk of renal impairment [25]. In this study, lamivudine and telbivudine were given as prophylactic antiviral therapy because entecavir was not

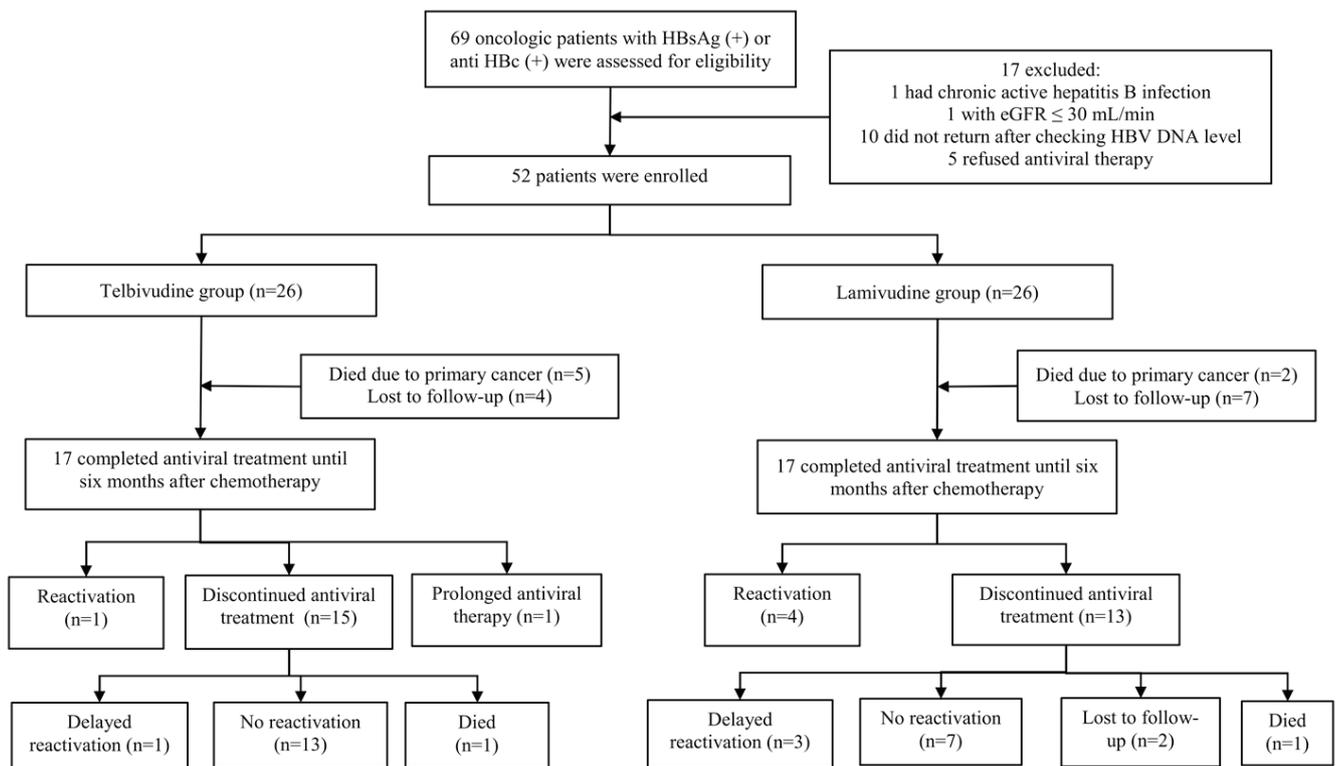


Figure 1. Flow diagram showing patient selection and outcome of antiviral prophylaxis

Table 1. Baseline characteristics

Characteristics	Telbivudine Group (n=26)	Lamivudine Group (n=26)
<b>Sex, n (%)</b>		
Male	14 (53.8)	7 (26.9)
Female	12 (46.2)	19 (73.1)
<b>Cancer type, n (%)</b>		
Non-Hodgkin Lymphoma	10 (38.5)	7 (26.9)
Breast cancer	8 (30.8)	10 (38.5)
Nasopharyngeal carcinoma	3 (11.5)	2 (7.7)
Seminoma	1 (3.8)	2 (7.7)
Colorectal cancer	2 (7.7)	1 (3.8)
Squamous cell carcinoma of head and neck	1 (3.8)	0 (0)
Cervical cancer	0 (0)	3 (11.5)
Rhabdomyosarcoma	0 (0)	1 (3.8)
Lung cancer	1 (3.8)	0 (0)
<b>Hepatitis B serology, n (%)</b>		
HBsAg (+), anti-HBc (+)	20 (76.9)	23 (88.5)
HBsAg (-), anti-HBc (+)	6 (23.1)	3 (11.5)
<b>Baseline HBV DNA, n (%)</b>		
High (≥2000 IU/mL)	8 (30.8)	17 (65.4)
Low (<2000 IU/mL)	18 (69.2)	9 (34.6)
<b>Chemotherapy regimen, n (%)</b>		
Rituximab-based	9 (34.6)	5 (19.2)
Others	17 (65.4)	21 (80.8)
<b>Duration of treatment (days)</b>		
Median	326	259
Range (min-max)	96-491	30-465

ALT: alanine aminotransferase, anti-HBc: anti-hepatitis B core, HbsAg: hepatitis B surface antigen

**Table 2.** Occurrence and outcome of hepatitis B reactivation during systemic cytotoxic chemotherapy (SCC)

Group	No. patient	Cancer Type	Status of HBsAg	Chemo-therapy regimen	Log10 [HBV DNA level] (IU/mL) at baseline	Log10 [HBV DNA level] (IU/mL) at reactivation	Time of reactivation	ALT at re-activation (U/L)	Degree of hepatitis	Follow up	Disruption of chemo-therapy	Outcome
Lami- vudine	1	Cervical cancer	Positive	Carboplatin	3.35	4.52	Six months after cessation of chemotherapy	27	Mild	HBV DNA level decreased spontaneously (log 2.91) three months after reactivation	No	Survive
	2	Breast cancer	Positive	Docetaxel, cyclophosphamide	1.33	2.65	Six months after cessation of chemotherapy	34	Mild	Continued LAM for one month than lost-to-follow up	No	Lost to follow-up
	3	Breast cancer	Positive	Docetaxel, cyclophosphamide	Undetectable	1.7	Six months after cessation of chemotherapy	6	Mild	Discontinued LAM, refused to undergo next cycle of chemotherapy	No	Mortality due to primary disease
	4	Non-Hodgkin lymphoma	Positive	R-CHOP	Undetectable	5.43	Three months after cessation of antiviral prophylaxis	262	Severe	Switched to tenofovir	No	Survive
	5	Breast cancer	Positive	Docetaxel, cyclophosphamide	4.31	8.23	Six months after cessation of chemotherapy	288	Severe	Switched to tenofovir	No	Survive
	6	Nasopharyngeal carcinoma	Positive	Cisplatin, 5-FU, Docetaxel	2.53	5.94	Week 24 (during chemotherapy)	21	Mild	Switched to tenofovir	No	Survive
	7	Breast cancer	Positive	Docetaxel, cyclophosphamide	Undetectable	3.72	One year after cessation of antiviral prophylaxis	94	Moderate	Switched to tenofovir	No	Survive
Telbi- vudine	1	Non-Hodgkin lymphoma	Negative	R-CHOP	Undetectable	1.78	Week 12 (during chemotherapy)	9	Mild	Continued telbivudine, HBV DNA became undetectable at week-24	No	Survive
	2	Non-Hodgkin lymphoma	Positive	R-CHOP	Undetectable	8.35	Three months after cessation of antiviral prophylaxis	375	Severe	Switched to tenofovir	No	Survive

ALT: alanine aminotransferase, DNA: deoxyribonucleic acid, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, 5FU: fluorouracil

available in our hospital and tenofovir started to be available in July 2016. Therefore, some patients who got hepatitis B reactivation were given tenofovir as salvage therapy (**Table 2**).

In our study, less incidence of HBV reactivation was found in the telbivudine group compared with the lamivudine group. In the telbivudine group, patients

with HBV reactivation had received a rituximab-containing chemotherapy regimen. Meanwhile, in the lamivudine group, patients with HBV reactivation had various underlying malignancies, i.e., breast cancer, cervical cancer, NHL, and nasopharyngeal carcinoma (**Table 2**). The risk of HBV reactivation with rituximab in patients with post exposures to hepatitis B (HBsAg-

negative, anti-HBc-positive) was estimated to be as high as 16.9% [26], while the relative risk of HBV reactivation in HBsAg-positive patients receiving rituximab-based regimen was 1.63 when compared with the control population [27]. In breast cancer patients treated with anthracycline-based therapy, HBV reactivation developed in 18.1% of patients [26].

Lamivudine prophylaxis is known to be safe and effective in preventing HBV reactivation in patients with non-Hodgkin lymphoma (NHL) under rituximab treatment and resolved HBV infection [28]. Of 85 patients with HBsAg negative/anti-HBc positive NHL patients, only one patient had HBV reactivation 31 months after stopping LMV due to the administration of another immunosuppressive drug. Lamivudine prophylaxis was associated with a lower risk for HBV reactivation and HBV-related death compared to no prophylaxis [13]. However, when compared with entecavir, treatment with lamivudine was associated with more incidence of HBV reactivation (7% vs 0%) in patients with solid tumors and positive HbsAg [29].

In this study, reactivation occurred during chemotherapy in two patients and between six months after completion of chemotherapy in four patients. According to the AASLD guidelines in 2009, it is recommended that patients with baseline HBV DNA < 2000 IU/mL be given prophylactic antiviral therapy for six months after the completion of chemotherapy, while those with baseline HBV DNA > 2000 IU/mL continue their treatment as immunocompetent patients. However, a longer treatment duration of 12 months after the completion of chemotherapy was recommended by recent APASL [9] and EASL guidelines [12]. Patients receiving a rituximab-based regimen were even recommended to receive an 18-month duration of antiviral prophylaxis [12]. Low baseline HBV DNA was noticed in 6 of 9 patients with HBV reactivation in our study. Furthermore, of the 6 patients with low HBV DNA, 5 patients had undetectable baseline HBV DNA. Thus, our findings support the latest recommendation by APASL and EASL to give antiviral prophylaxis for a minimum of 12 months.

Severe hepatitis with an ALT level above 200 U/L and a high level of HBV DNA at reactivation was encountered in 3 of 9 patients; two of them received a rituximab-containing regimen, and both had delayed reactivation. In patients undergoing chemotherapy, a hundredfold rise in serum HBV DNA may precede serum ALT elevation by 12 to 28 weeks [30]. This late onset of clinical hepatitis could be attributed to delayed immune recovery related to prolonged suppressive effects of rituximab [31]. In breast cancer patients receiving doxorubicin, cyclophosphamide, and dexamethasone premedication, serum HBV DNA peaked

prior to ALT by nearly two weeks [32]. However, we had three breast cancer patients who got hepatitis B reactivation six months after cessation of chemotherapy (at the end of antiviral prophylaxis) and one breast cancer patient experiencing delayed hepatitis B reactivation at one year after cessation of antiviral prophylaxis. Therefore, regular testing of HBV DNA level every 3 to 6 months during prophylaxis and for at least 12 months after NA withdrawal is of foremost importance.

There are several limitations to our study. As this is a retrospective cohort study with a small number of patients and heterogeneous characteristics, we could not analyze the difference of HBV reactivation incidence between both groups statistically. Low patient survival and low patient compliance were some obstacles that prevented us from conducting a long observation. Furthermore, the drug resistance profile of patients with HBV reactivation was not studied. However, considering the various durations of cancer chemotherapy, telbivudine and lamivudine may become first-line therapies for those who are expected to use antiviral prophylaxis for less than one year or those with undetectable HBV DNA. Despite all the limitations above, we have added scientific data on the use of telbivudine or lamivudine as hepatitis B prophylaxis in patients undergoing chemotherapy or treatment with B-cell depleting agents, such as rituximab. Further research comparing antivirals with the higher barrier of resistance, such as tenofovir or entecavir, in patients treated with immunosuppressive therapy, is needed to determine the best strategy for the prevention of hepatitis B reactivation.

## CONCLUSIONS

Preemptive telbivudine or lamivudine administration in HBsAg positive or HBsAg negative and anti-HBc positive patients seems to be a good treatment option.

## DECLARATIONS

### Competing of Interest

The authors have no conflicts of interest to declare.

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