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Original Article

Lamivudine versus entecavir in the rescue of chemotherapy-induced hepatitis B flare-up

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Abstract

Background: Lack of nucleos(t)ide analogue (NA) prophylaxis prior to chemotherapy is a common problem worldwide. The efficacy of newer-generation NAs in the rescue for the hepatitis B virus (HBV) reactivation has not been confirmed. We aimed to compare lamivudine (LVD) and entecavir (ETV) in the rescue of chemotherapy-induced HBV flare-up.

Methods: In this retrospective cohort study, we screened all HBV carriers who received therapeutic LVD or ETV for hepatitis flare-up after chemotherapy between January 1, 2004 and December 31, 2015. Patients who had other concurrent primary liver diseases such as chronic hepatitis C, who had baseline HBV viral load <2000 IU/ml or data unavailable, or those who had primary or secondary liver cancers were excluded. By means of propensity scores, LVD users were randomly matched 1:1 with ETV users. Cumulative incidences of, and hazard ratios (HRs) for, mortality at 6 months were analyzed, and 1-year virological responses were evaluated.

Results: In total, 32 LVD and 32 ETV users were matched for outcome analysis, and their baseline characteristics were not significantly different. Comparing LVD users to ETV users, the 6-month liver-related mortality rates (6.3% vs. 12.5%, $p = 0.47$) and overall mortality rates (31.3% vs. 25%, $p = 0.54$) were not significantly different. In multivariate analysis, prothrombin time prolongation >4 s (HR: 10.78, 95% confidence interval [CI]: 1.55–74.93) and HBV viral load L (HR: 3.40 per 1 log IU/ml, 95% CI: 1.39–8.40) were independent prognostic factors for liver-related mortality. There was no drug resistance to LVD or ETV over the course of 1 year.

Conclusion: Clinical outcomes were not different between LVD and ETV users. Delayed detection of hepatitis flare-up with coagulopathy and a high viral load could result in a poor prognosis.

Keywords: Chemotherapy; Hepatic failure; Immunosuppression; Nucleoside; Nucleotide

1. Introduction

Hepatitis B reactivation induced by immunosuppressive or cytotoxic chemotherapy is common among hepatitis B virus (HBV) carriers, and the prevalence has been reported to be as high as 20–50%.[1] Hepatitis B reactivation not only necessitates delay in the chemotherapy schedule or premature termination of treatment, but also results in hepatic failure and death in 5%–40% of HBV carriers.[2,3] Prophylactic antivirals can reduce the chance of HBV reactivation and patient mortality, and international guidelines have recommended antiviral prophylaxis before the start of chemotherapy.[1,4,5] However, many HBV carriers don't receive prophylactic antivirals before chemotherapy due to the high cost of drugs,

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lack of insurance coverage, lack of awareness of the patient's condition or neglect by physicians.[6–10] Even in developed countries, the screening rate of HBV infection for newly-diagnosed cancer patients who will receive chemotherapy may be less than 20%.[7] Due to a lack of antiviral prophylaxis worldwide, prompt antiviral rescue for chemotherapy-induced hepatitis B flare-up remains a critical issue.

Chemotherapy-induced hepatitis B flare-up is involved in rapidly increased viral replication in the immunosuppression phase, and extensive destruction of infected hepatocytes during restoration of immunity after chemotherapy.[11] Although urgent antiviral therapy has until now been the only reliable way to rescue hepatitis flare-up, some patients will still die from hepatic failure.[12–14] Most of the data on therapeutic antivirals are included in studies of patients who took lamivudine (LVD). However, newer-generation nucleos(t)ide analogues (NAs) with stronger antiviral potency than LVD, such as entecavir (ETV), have been developed.[15] Although ETV has been shown to successfully achieve control of hepatitis B flare-up following chemotherapy in a few case reports,[14,16,17] the efficacy and safety of ETV when applied to severe hepatitis B flare-up is still controversial.[18] In a study of chronic hepatitis B patients with spontaneous acute exacerbation, ETV was correlated with a higher mortality rate when compared to LVD.[19] Although newer-generation NAs have been widely used towards the treatment of chronic hepatitis B, their application for use in chemotherapy-induced hepatitis B flare-up requires further clarification.

Having the desirable advantage of possessing low drug resistance rates, newer-generation NAs, such as ETV, have been recommended for long-term use in the management of chronic hepatitis B.[4,20] However, according to results from previous studies of chronic hepatitis B patients with spontaneous acute exacerbation, the drug resistance rate of LVD was relatively lower than that of patients with general chronic hepatitis. Data is limited, so we are still no certain if drug resistance remains an important issue when choosing NAs for cancer patients with chemotherapy-induced hepatitis B flare-up.[21] To date, no study has compared the efficacy and safety of various NAs in the management of chemotherapy-induced hepatitis B flare-up. The aim of this study was to compare the treatment outcomes of LVD and ETV users.

2. Methods

2.1. Study design

This retrospective cohort study was conducted at Taichung Veterans General Hospital, a tertiary referral center located in central Taiwan. All patients who were referred by oncologists as being diagnosed as chemotherapy-related hepatitis B flare-up were analyzed for eligibility from January 1, 2004 to December 31, 2015. The protocol of the present study was approved by the Institutional Review Board of Taichung Veterans General Hospital (No. CE13100).

2.2. Study cohort

The process of patient selection is presented in Fig. 1. We screened all HBV carriers who were treated with LVD and ETV for hepatitis flare-up after undergoing chemotherapy. Hepatitis flare-up after chemotherapy was defined as follows: HBV carriers who had a serum alanine aminotransferase level of more than 2 times the baseline ALT, and more than 2 times the upper limit of normal levels after chemotherapy. Patients were excluded if they received NAs for chronic hepatitis B before chemotherapy, received concurrent glucocorticoid therapy for causes other than chemotherapy, had other concurrent primary liver diseases (such as chronic hepatitis C, hepatitis D, autoimmune hepatitis, or Wilson's disease), or who had metastatic or primary malignant liver tumors. In addition, patients with serum HBV DNA <2000 IU/ml before receiving NAs or unavailable data were also excluded. Only

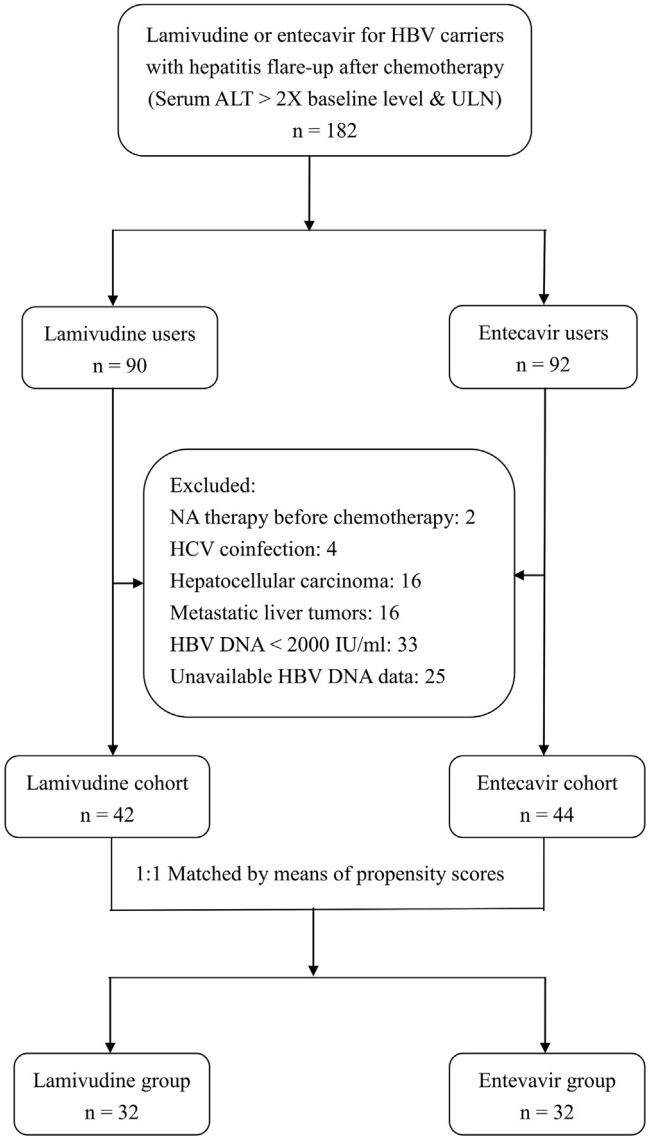

Fig. 1. Selection of study subjects. ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = nucleos(t)ide analogue; ULN = upper limit of normal.

LVD was reimbursed by the Taiwan's National Health insurance (NHI) before August 2008, and either LVD or ETV can be chosen by physicians afterward. With the advantages in high antiviral efficacy and low viral resistance rate, physicians tended to prescribe ETV rather than LVD, so ETV was used for most patients (83%) after August 2008 in this study. By means of propensity scores composed from age, sex, hepatitis B e antigen (HBeAg) positivity, baseline HBV viral load, baseline bilirubin level, and baseline ALT level, LVD users were randomly matched 1:1 with ETV users.

2.3. Outcome analysis

Baseline characteristics were recorded as the day that antiviral therapy commenced. Cumulative incidences of liver-related mortality and overall mortality at 6 months were calculated. In addition, patient proportions of serum ALT normalization (biochemical response), undetectability of HBV DNA (virological response), along with the emergence of drug resistance were determined one year after antiviral rescue therapy. Virological response was defined as HBV DNA level <20 IU/ml in blood. Drug resistance was defined as a 10-fold increase of blood HBV DNA levels under good drug compliance.

2.4. Statistical analysis

Categorical variables presented as numbers and percentages were compared by Fisher's exact test. Continuous variables presented as median and interquartile range (IQR), were compared by use of the Mann−Whitney U test. HBV DNA was logarithmically transformed to normal distribution for analysis. Kaplan−Meier survival curves of the two treatment groups were plotted and compared by using the log-rank test. Prognostic factors associated with liver-related mortality were analyzed by the Cox proportional hazards model. Two-tailed p values <0.05 were considered to be statistically significant. Statistical tests were performed by using the Statistical Package for the Social Sciences (version 15.1; SPSS, Inc., Chicago, IL, USA) & SAS (version 9.1.3).

3. Results

3.1. Study subject

As shown in Fig. 1 and 182 HBV carriers with hepatitis flare-up after chemotherapy were screened. In total, 96 patients were excluded according to the exclusion criteria, including 2 patients who initiated NA therapy before chemotherapy, 4 patients with HCV co-infection, 16 patients with hepatocellular cell carcinoma, 16 patients with metastatic liver tumors, 33 patients with baseline serum HBV DNA level <2000 IU/ml, and 25 patients whose HBV DNA data was not available. As shown in Supplementary Table 1, the baseline demographic characteristics in both treatment cohorts were generally not significantly different before propensity score matching; except higher values of AST, ALT, and MELD score in the LVD cohort, and more patients who received hydroxydaunorubicin-containing chemotherapy in the ETV cohort. Finally, by means of calculating propensity scores, 32 LVD users were randomly matched with 32 ETV users for outcome analysis.

After propensity score matching (Table 1), the baseline characteristics in both treatment groups were not significantly

Table 1
Baseline characteristics of patients with chemotherapy-induced hepatitis B flare-up.

Characteristics	Lamivudine (n = 32)	Entecavir (n = 32)	p
Age, years	55.5 (46.5−63.8)	55.5 (48.5−70)	0.42
Male gender, n (%)	25 (78.1)	22 (68.8)	0.57
ALT before chemotherapy, U/l	29 (19.5−41.3)	33.5 (19−47)	0.40
Underlying cirrhosis, n (%)	1 (3.1)	0	1.00
Underlying malignancy, n (%)			
Lung cancer	9 (28.1)	6 (18.8)	0.56
Head & Neck	7 (21.9)	3 (9.4)	0.30
Lymphoma	4 (12.5)	5 (15.6)	1.00
Breast cancer	2 (6.3)	5 (15.6)	0.43
Colon cancer	2 (6.3)	5 (15.6)	0.43
Leukemia	4 (12.5)	1 (3.1)	0.36
Esophageal cancer	0 (0)	3 (9.4)	0.24
Others[a]	4 (12.5)	4 (12.5)	1.00
Chemotherapy, n (%)			
Cisplatin	17 (53.1)	15 (46.9)	0.80
5-FU	8 (25)	13 (40.6)	0.29
Cyclophosphamide	8 (25)	8 (25)	1.00
Vincristine	7 (21.9)	3 (9.4)	0.30
Hydroxydaunorubicin	1 (3.1)	7 (21.9)	0.06
Rituximab	3 (9.4)	5 (15.6)	0.71
Glucocorticoid	3 (9.4)	7 (21.9)	0.30
Length of chemotherapy,[b] days	62 (34−158)	56.5 (29.75−104.75)	0.64
Time to hepatitis flare-up,[c] days	16 (13.3−43.5)	16.5 (8.5−30.5)	0.30
Time to antiviral therapy,[d] days	6 (2−13)	5 (2−11.5)	0.78
Positive HBeAg, n (%)	7 (21.9)	4 (12.5)	0.51
HBV viral load, log IU/ml	6.12 (4.3−7.3)	6.4 (4.4−7.6)	0.53
AST, U/l	289 (116.3−460.8)	199.5 (42.5−444.3)	0.27
ALT, U/l	355 (164.3−833)	258 (73.5−614.3)	0.21
Bilirubin-T, mg/dl	0.7 (0.5−1.5)	0.8 (0.5−1.0)	0.65
PT prolongation, seconds	0.6 (0−2.2)	0.6 (0−1.2)	0.89
Albumin, g/dl	4.0 (3.3−4.2)	3.7 (3.3-4.0)	0.13
Creatinine, mg/dl	1.0 (0.8−1.4)	0.9 (0.8−1.2)	0.60
Child-Pugh score	6 (5−6)	5 (5−6)	0.30
MELD score	10 (7−15)	7 (7−10)	0.13

The continuous variables are presented as median (25−75% interquartile).
AST = aspartate aminotransferase; ALT = alanine aminotransferase; HBV = hepatitis B virus; HBeAg = hepatitis B e antigen; PT = prothrombin time.
[a] One brain tumor, one cervical cancer, one multiple myeloma, one myxofibrosarcoma, one prostate cancer, one unknown primary adenocarcinoma, and two endometrial cancer.
[b] Length of chemotherapy: duration from the first chemotherapy to last chemotherapy.
[c] Time to hepatitis flare-up: duration from most recent chemotherapy to hepatitis flare-up.
[d] Time to antiviral therapy: duration from hepatitis flare to the initiation of antiviral treatment.

different. Most patients were middle-aged men without HBeAg positivity, and only one patient in the LVD group had underlying cirrhosis of Child-Pugh class A. The majority of patients possessed normal liver function prior to the start of chemotherapy, and the median ALT before chemotherapy was not significantly different between LVD and ETV users (29 vs. 33.5 U/l, $p = 0.4$). The patient proportions of underlying malignancies were not significantly different in both groups, where lung cancer was the most common malignancy. Cisplatin, 5-FU, cyclophosphamide, vincristine, glucocorticoid, hydroxydaunorubicin and rituximab were the most commonly used chemotherapy regimens. The median length of chemotherapy was not significantly different between the LVD and ETV users (62.0 vs. 56.5 days, $p = 0.64$).The majority of patients received regularly scheduled follow-ups for liver function analysis every 2–4 weeks after the administration of chemotherapy. The results showed that the median duration of time to hepatitis flare-up (from the most recent chemotherapy to hepatitis flare-up) was not significantly different between LVD and ETV users (16.0 vs. 16.5 days, $p = 0.30$). Antivirals were usually administered within one week after hepatitis flare-up. The differences of hepatitis status at the time of hepatitis flare-up between LVD and ETV users were not statistically significant. The median ALT level was greater than 5 times that of the ULN, but liver function was usually still compensated with normal median values of bilirubin-total and prothrombin time (PT). The median HBV DNA level was higher than 10^6 IU/ml.

3.2. Liver-related mortality and overall mortality

As shown in Supplementary Table 2, the rates of liver-related mortality and overall mortality were basically not significantly different between the two treatment cohorts before propensity score matching. Comparing LVD users to ETV users, the 6-month liver-related mortality rates (7.1% vs. 13.6%; p = 0.41) were not significantly different. After propensity score matching (Table 2), the rates of liver-related mortality and overall mortality remained not significantly different between LVD and ETV users over the course of 1, 3, 6, and 12 months. In total, 2 LVD users and 4 ETV users died of hepatic failure, and each died within three months of hepatitis flare-up. As shown in Fig. 2A, the cumulative incidences of liver-related mortality within 6 months were not significantly different between LVD and ETV users (6.3% vs. 12.5%; $p = 0.47$). Moreover, as shown in Fig. 2B, the 6-month overall mortality rates were also not significantly different between LVD and ETV users (31.3 vs. 25%, $p = 0.54$). Mortality after recovery from hepatitis B flare-up was caused by underlying malignancies.

3.3. Prognostic factor analysis for liver-related mortality

Before propensity score matching (Supplementary Table 3), baseline PT prolongation, high HBV viral load, ALT elevation, and bilirubin elevation were related to liver-related mortality in univariate regression analysis. However, in multivariate regression analysis, only PT prolongation (HR: 1.21 per 1 s, 95% CI: 1.04–1.41) and HBV viral load (HR: 2.51 per 1 log IU/ml, 95% CI: 1.44–4.36) were independent prognostic factors for liver-related mortality.

Table 2
Clinical outcomes of lamivudine and entecavir users.

Outcome, n (%)	Lamivudine (n = 32)	Entecavir (n = 32)	p
Overall mortality			
Death within 1 month	5 (15.6)	1 (3.1)	0.09
Death within 3 months	7 (21.9)	7 (21.9)	0.90
Death within 6 months	10 (31.3)	8 (25.0)	0.54
Death within 12 months	14 (43.8)	13 (40.6)	0.67
Cause of death (within 1 month)			
Liver failure	2 (6.3)	1 (3.1)	0.52
Non-liver failure	3 (9.4)	0 (0)	0.73
Cause of death (within 3 months)			
Liver failure	2 (6.3)	4 (12.5)	0.47
Non-liver failure	5 (15.6)	3 (9.4)	0.43
Cause of death (within 6 months)			
Liver failure	2 (6.3)	4 (12.5)	0.47
Non-liver failure	8 (25.0)	4 (12.5)	0.21
Cause of death (6 months to 12 months)			
Liver failure	0	0	
Non-liver failure	4 (12.5)	5 (15.6)	0.90

After propensity score matching (Table 3), in univariate regression analysis, baseline PT-related parameters, such as PT prolongation in seconds (hazard ratio [HR]: 1.23, 95% confidence interval [CI]: 1.06–1.42), PT prolongation > 3 s (HR: 7.78, 95% CI: 1.56–38.88), PT prolongation > 4 s (HR: 13.73, 95% CI: 2.73–69.09), and MELD score (HR: 1.18, 95% CI: 1.05–1.32), were associated with liver-related mortality. In addition, elevated baseline HBV viral load was also related to liver-related mortality (HR: 4.07 per 1 log IU/ml, 95% CI: 1.70–9.74). For avoiding the strong collinearity between PT and MELD score in multivariate regression analysis, we respectively conducted two models in the Table 3: In the model 1, baseline PT prolongation >4 s (HR: 10.78, 95% CI: 1.55–74.93) and elevated HBV viral load (HR: 3.40 per 1 log IU/ml, 95% CI: 1.39–8.40) were independent prognostic factors associated with liver-related mortality. However, in the model 2, after adjusting for HBV viral load, MELD score became not an independent prognostic factor related to liver-related mortality (HR: 1.16, 95% CI: 0.99–1.36).

3.4. Biochemical and virological responses

We analyzed the biochemical and virological responses of patients who survived longer than one year after chemotherapy-related hepatitis B flare-up. During the one-year follow-up period, 14 patients in the LVD cohort and 13 patients in the ETV cohort died, and a small proportion of patients (3 LVD users and 2 ETV users) were lost of follow-up. Finally, 15 patients in the LVD cohort and 17 patients in the ETV cohort were enrolled for the analysis of biochemical and virological response in one year. Among 15 LVD users and 17 ETV users, the proportion of ALT normalization was not significantly different after antiviral treatment over the course of one year (LVD vs. ETV: 86.67% vs. 94.12%, $p = 0.68$). In

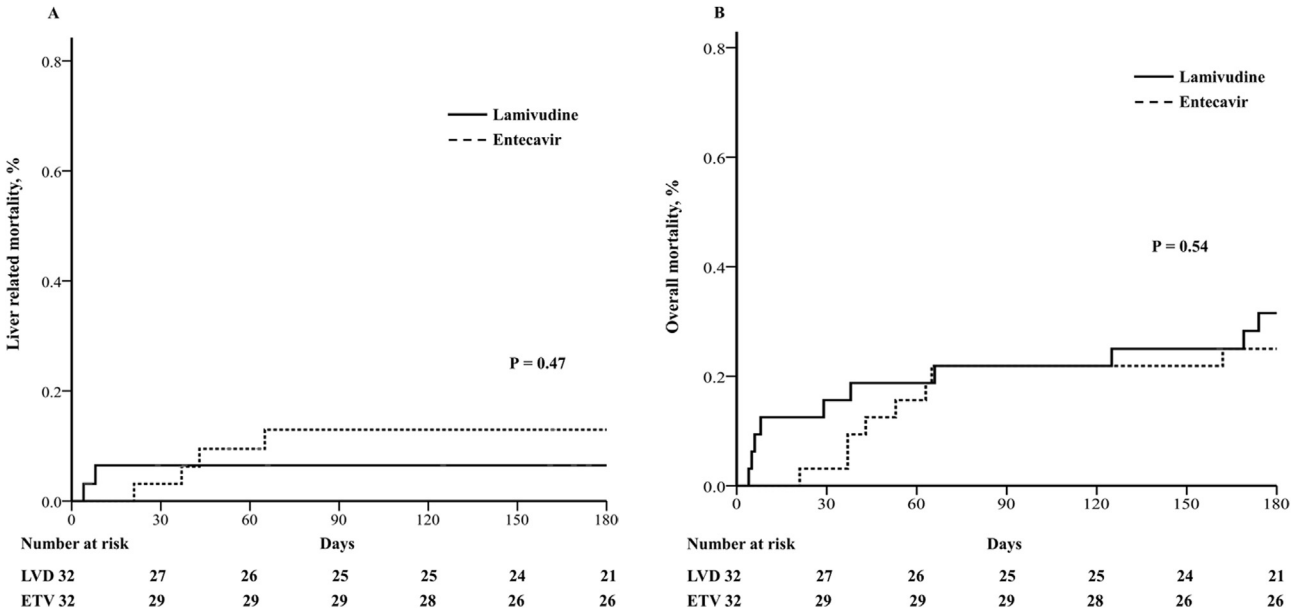

Fig. 2. Cumulative incidences of patient mortality: (A) liver-related mortality, (B) overall mortality in 6 months.

Table 3
Predictive factors associated with liver-related mortality.

Variable	Univariate analysis			Multivariate model 1			Multivariate model 2		
	HR	95 % CI	*p*	HR	95 % CI	*p*	HR	95% CI	*p*
Entecavir use	1.85	0.34–10.09	0.48						
Age, year	1.03	0.96–1.09	0.43						
Male gender	33.08	0.02–67,898.06	0.37						
ALT before chemotherapy, U/l	0.98	0.92–1.03	0.36						
Positive HBeAg	0.36	0.00–238.95	0.46						
Time to antiviral therapy, day	0.98	0.89–1.09	0.71						
HBV DNA, log IU/ml	4.07	1.70–9.74	<0.01	3.40	1.39–8.40	<0.01	3.34	1.45–7.69	<0.01
ALT, U/l	1.00	1.00–1.00	0.33						
ALT > 10X ULN	2.93	0.54–15.99	0.22						
PT prolongation, second	1.23.	1.06–1.42	0.01						
PT prolong >3 seconds	7.78	1.56–38.88	0.01						
PT prolong >4 seconds	13.73	2.73–69.09	<0.01	10.78	1.55–74.93	0.02			
Bilirubin, mg/dl	1.12	0.91–1.38	0.30						
Bilirubin > 2X ULN	1.87	0.22–15.99	0.57						
Albumin, g/dl	1.18	0.21–6.56	0.85						
Creatinine, mg/dl	1.53	0.19–12.42	0.69						
MELD score	1.18	1.05–1.32	<0.01				1.16	0.99–1.36	0.07
Glucocorticoid	2.52	0.46–13.76	0.29						

ALT = alanine aminotransferase; CI = confidence interval; HBeAg = hepatitis B e antigen; HR = hazard ratio; PT = prothrombin time.

addition, LVD and ETV users were not significantly different in attaining HBV undetectability (80% vs. 75%, $p = 1.00$), and no drug resistance to LVD or ETV was detected in one year.

4. Discussion

Our study reconfirmed that patients may die of chemotherapy-related hepatic failure even under newer-generation NAs with strong antiviral potency; hence screening for HBV infection prior to chemotherapy and antiviral prophylaxis are mandatory as the recommendations in the international practice guidelines of the Associations of the Study of Liver Disease.[1,4,5] However, prophylactic NA therapy might not be prescribed by various reasons in the real world. For example, rescue NA therapy for hepatitis B reactivation after chemotherapy has been reimbursed by the Taiwan's NHI since 2004, but the reimbursement of antiviral prophylaxis was not included until November 2009. In this study, most patients (55.8%) were enrolled prior to 2010, and only few patients (2.3%) were included in the last year of study period (2015). In addition, the HBV screening rate needs to be improved. In a study conducted at a medical center in Taiwan, the HBV screening rate was only 40.2% from August 2010 to July 2012, but the screening rate was increased up to 99.3% after

introducing a computerized order entry–based therapeutic control system in August 2012.[22,23] The improvement in HBV screening rate was similar in our hospital. However, we believe that the computerized control system may not be available in many hospitals, and this study can remind physicians, health care providers or systems the importance of antiviral prophylaxis.

Lack of antiviral prophylaxis is not a rare condition in daily practice, even in developed countries,[6,7,22,24] and HBV carriers may suffer from severe hepatitis B flare after chemotherapy. To the best of our knowledge, the present study is the first attempt to compare the efficacy of LVD and ETV in the rescue of chemotherapy-induced hepatitis B flare-up, and we found that both liver-related mortality rates and overall mortality rates were not significantly different. However, the degrees of PT prolongation and viral load elevation at the time of initiating antiviral treatment were independent prognostic factors for poor outcomes. To improve patient outcomes, our data suggested that hepatitis B flare-up needs to be detected as early as possible after chemotherapy, and antiviral therapy, either LVD or ETV, should be administrated as soon as possible. Therefore, for HBV carriers who do not receive NA prophylaxis before chemotherapy, we recommend a close monitoring of their liver function and/or HBV viral load. In some regions or countries where HBV DNA monitoring may not be affordable or available, liver function should be monitored at least.

Even though ETV can achieve greater viral suppression than LVD in the treatment of chronic hepatitis B, ETV was not found to be superior in treating chemotherapy-induced hepatitis B flare-up. Patients who died of hepatic failure expired within 3 months of initiating antiviral therapy, so the speed of viral suppression may not be fast enough to rescue patients experiencing liver decompensation with a high viral load. The findings of our study were comparable with those of a previous study performed on HBV carriers with spontaneous severe acute exacerbation,[25] whose authors reported that antiviral therapy may be ineffective once severe liver decompensation has developed. Our findings support that early detection of a hepatitis flare-up may be more valuable than initiating the use of more potent antiviral drugs. In addition, in a previous study of HBV carriers with spontaneous severe acute exacerbation, ETV was reported to independently increase short-term mortality (HR: 5.1, 95% CI: 1.5–17.2), despite it offering more rapid viral suppression along with higher virological and biochemical response rates at 6 months when compared to LVD treatment.[19] The reasons that ETV treatment impaired short-term outcomes are not fully understood. Additional reason might be deferring an effective drug concentration in hemodynamics or fatal lactic acidosis.[26] In contrast, previous studies reported similar clinical outcomes between ETV and LVD when treating decompensated chronic hepatitis B.[25,27] In our study, we did not find any significant outcome differences between ETV and LVD users, and our data did not support a hesitation break in the use of ETV. Further studies in different clinical scenarios may help in clarifying the overall treatment scenario.

ETV has been known to have a stronger potency in handling HBV inhibition than that of LVD.[8] However, LVD and ETV did not show significantly different results in attaining both ALT normalization and HBV undetectability over the course of one year during this study. Drug resistance is a critical consideration when choosing antiviral agents, particularly for chronically ill patients. ETV users have been shown to have much lower drug resistance rates than LVD users in the management of chronic hepatitis B.[8,20] However, unlike the HBV-specific immune dysfunction in chronic hepatitis B, chemotherapy-related hepatitis B flare-up usually occurs as a strong immune rebound response after withdrawal from immunosuppression.[28] In a prospective study of patients with non-Hodgkin's lymphoma, HBV carriers were randomly placed in either a prophylactic LVD or therapeutic LVD group prior to chemotherapy, where no patients in the therapeutic group developed any drug resistance over a 12-month period.[21] Compatible with the results in our study, no patient in either group developed drug resistance over the course of one year. Similar findings were also reported in chronic hepatitis patients with spontaneous acute exacerbation, where the rates of drug resistance to LVD were lower than the norm.[29] Therefore, drug resistance may not be an important issue with regards to short-term outcomes when choosing LVD or ETV treatment. Here, LVD could be considered as an alternative for cancer patients with a shorter life expectancy. However, if patients require long-term use of NAs after chemotherapy, additional data is needed, which will necessitate further investigation.

The effect of individual chemotherapy regimen on HBV reactivation may be different. For example, rituximab has been associated with fulminant hepatitis B flare, hepatic failure and mortality, even in resolved HBV infection, and current guidelines strongly suggested antiviral prophylaxis in rituximab treated patients.[4,5,30] Although our hematologists had painful experiences on the use of rituximab,[31] antiviral prophylaxis might not be prescribed before the NHI reimbursement of antiviral prophylaxis. Moreover, although glucocorticoid-containing chemotherapy may improve patient survival on cancer control, such as the prednisolone combination for lymphoma, steroid therapy could also result in severe HBV flare.[32] The prognostic effect of glucocorticoid in cancer patients with HBV flare after chemotherapy remains unclear. In this study, glucocorticoid was not an independent prognostic factor associated with liver–related mortality (HR: 2.52, 95% CI: 0.46–13.76, $p = 0.29$) or overall mortality (HR: 0.99, 95% CI: 0.29–3.38, $p = 0.98$). However, due to the wide variations in malignancies and chemoagent complexes in this study, the prognostic role of individual regimen needs other specified study designs for further confirmation.

There are several limitations in the present study. First, this study reflected the experience of a single medical center, providing a relatively small sample size. However, this study did report the largest cohort in the comparison of NAs for chemotherapy-related hepatitis B flare-up to date. Still, research involving larger sample sizes should be encouraged for further confirmation. Second, this study was of a retrospective design. Some data comprised of potential confounders, such as HBV genotypes, were lacking.

Investigations involving other potential confounders will be helpful in order for a complete evaluation to be made. Third, differentiating hepatitis B flare-up from drug toxicity due to chemotherapy could be sometimes difficult in clinical practice. However, patients with a DNA viral load <2000 IU/ml were excluded in this study, so we believe that the risk of an incorrect diagnosis of hepatitis B flare has been minimized. Lastly, we did not enroll patients who received other NAs, such as telbivudine or tenofovir, because of the small case numbers. Although different NAs (LVD and ETV) were equally effective in this study, investigations with additional NAs could prove to be important for confirmation.

In conclusion, short-term clinical outcomes were not significantly different between LVD and ETV users with chemotherapy-induced hepatitis B flare-up. Delayed detection of hepatitis flare-up with concomitant coagulopathy and high viral load could result in poor prognosis regardless of whether LVD or ETV is administered. Drug resistance may not prove to be an important issue regarding short-term outcomes when choosing LVD or ETV, and LVD may well be an alternative option for cancer patients with a shorter life expectancy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcma.2017.07.009.

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