Original Investigation

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

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IMPORTANCE Hepatitis B virus (HBV) reactivation is a serious complication for patients with lymphoma treated with rituximab-containing chemotherapies, despite lamivudine prophylaxis treatment. An optimal prophylactic antiviral protocol has not been determined.

OBJECTIVE To compare the efficacy of entecavir and lamivudine in preventing HBV reactivation in patients seropositive for the hepatitis B surface antigen with untreated diffuse large B-cell lymphoma receiving chemotherapy treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

DESIGN, SETTING, AND PATIENTS Randomized, open-label, phase 3 study conducted from February 2008 through December 2012 at 10 medical centers in China. This study was a substudy of a parent study designed to compare a 3-week with a 2-week R-CHOP chemotherapy regimen for untreated diffuse large B-cell lymphoma. Patients enrolled in the parent study who were seropositive for the hepatitis B surface antigen and had normal liver function, serum HBV DNA levels of less than 10^3 copies/mL, and no prior antiviral therapy were randomized to entecavir (n = 61) or lamivudine (n = 60).

INTERVENTIONS Daily entecavir (0.5 mg) or lamivudine (100 mg) beginning 1 week before the initiation of R-CHOP treatment to 6 months after completion of chemotherapy.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the incidence of HBV-related hepatitis. The secondary end points included rates of HBV reactivation, chemotherapy disruption due to hepatitis, and treatment-related adverse events.

RESULTS The date of last patient follow-up was May 25, 2013. Incidence of HBV-related hepatitis was significantly lower for the entecavir group vs the lamivudine group.

<table>
<thead>
<tr>
<th>Patients With Event, No. (%)</th>
<th>Entecavir (n = 61)</th>
<th>Lamivudine (n = 60)</th>
<th>Difference (95% CI), %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-related hepatitis</td>
<td>0 (0.0)</td>
<td>8 (13.3)</td>
<td>13.3 (4.7 to 21.9)</td>
<td>.003</td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>4 (6.6)</td>
<td>18 (30.0)</td>
<td>23.4 (10.2 to 36.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Chemotherapy disruption</td>
<td>1 (1.6)</td>
<td>11 (18.3)</td>
<td>16.7 (6.4 to 27.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td>15 (24.6)</td>
<td>18 (30.0)</td>
<td>5.4 (−10.3 to 21.3)</td>
<td>.50</td>
</tr>
</tbody>
</table>

CONCLUSIONS AND RELEVANCE Among patients seropositive for the hepatitis B surface antigen with diffuse large B-cell lymphoma undergoing R-CHOP chemotherapy, the addition of entecavir compared with lamivudine resulted in a lower incidence of HBV-related hepatitis and HBV reactivation. If replicated, these findings support the use of entecavir in these patients.

TRIAL REGISTRATIONS ClinicalTrials.gov Identifier: NCT01793844; Chinese Clinical Trial Registry Identifier: CTR-TRC-11001687


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**Methods**

**Patients**
This clinical trial was conducted between February 2008 and December 2012 at 10 medical centers in China. All patients were hospitalized during R-CHOP chemotherapy. Patients were eligible if they were at least 18 years of age; had newly diagnosed diffuse large B-cell lymphoma according to the World Health Organization classification; were seropositive for the hepatitis B surface antigen; had an Eastern Cooperative Oncology Group performance status of 3 or less; had a life expectancy of longer than 3 months; had adequate organ function, normal liver function (assessed by levels of alanine aminotransferase [ALT], aspartate aminotransferase, and bilirubin), and serum HBV DNA levels of less than 10^5 copies/mL; and had no prior use of antiviral therapy. Patients were excluded if they had primary central nervous system or testicular lymphoma, had a history of other malignancies, had other severe comorbidities, were lactating or pregnant, or had any other positive viral markers, such as IgM antibody to hepatitis A virus, hepatitis C virus viral load, IgG antibody to hepatitis D virus, IgM antibody to hepatitis E virus, or antibody to human immunodeficiency virus.

This study complied with all provisions of the Declaration of Helsinki and was conducted in accordance with good clinical practice guidelines. The protocol was approved by the ethical review committee of each participating center. All patients provided written informed consent.

**Study Design and Randomization**
This study was a substudy of a parent trial that compared a 3-week R-CHOP (R-CHOP-21) regimen with a 2-week R-CHOP (R-CHOP-14) regimen for treating patients with newly diagnosed diffuse large B-cell lymphoma (Supplement 1 and Supplement 2). Patients with untreated diffuse large B-cell lymphoma were randomly assigned to groups treated with R-CHOP-21 or R-CHOP-14 in a 1:1 ratio. Randomization was performed by an independent statistician using a computer-generated randomization schedule. The randomization code was provided in sealed envelopes. Patients enrolled in the R-CHOP-21 or R-CHOP-14 group who were seropositive for the hepatitis B surface antigen, had normal liver function, had serum HBV DNA levels of less than 10^5 copies/mL, and had no prior antiviral therapy use were randomized to receive prophylactic entecavir or lamivudine stratified in each separate group of the parent study according to a random sequence table. The treating physician prescribed the assigned treatment, and patients paid for the agent themselves. Therefore, investigators and patients were not blinded to treatment assignment. However, the data collection staff and the statistician were unaware of treatment assignment.

**Interventions**
The standard R-CHOP regimen for diffuse large B-cell lymphoma consisted of rituximab (375 mg/m^2 administered intravenously on day 1), cyclophosphamide (750 mg/m^2 administered intravenously on day 2), doxorubicin (50 mg/m^2 administered intravenously on day 2), vincristine (1.4 mg/m^2 up to a maximal dose of 2 mg, administered intravenously on day 2), and prednisone (60 mg/m^2/d for 5 days). The R-CHOP-21 regimen was administered every 3 weeks and the R-CHOP-14 regimen was administered every 2 weeks.
2 weeks. Patients with limited-stage diffuse large B-cell lymphoma, bulky disease, or any adverse risk factors (eg, a high lactate dehydrogenase level, stage II cancer, age >60 years, and Eastern Cooperative Oncology Group performance status of ≥2) received 6 cycles of R-CHOP chemotherapy followed by involved field radiation therapy, whereas patients without adverse risk factors received 3 to 4 cycles of R-CHOP chemotherapy followed by involved field radiation therapy. For advanced-stage disease, patients received 6 to 8 cycles of R-CHOP with radiation therapy added to residual disease.

Prophylactic entecavir (0.5 mg orally every day) or lamivudine (100 mg orally every day) was initiated 1 week before chemotherapy and withdrawn 6 months after completion of chemotherapy. Modification or resumption of antiviral treatment was allowed for patients who developed HBV reactivation or HBV-related hepatitis. Complete blood cell counts and liver and renal function tests were monitored before each chemotherapy cycle, every month after the cessation of chemotherapy for 6 months, and then every 3 to 6 months after the withdrawal of antiviral prophylaxis. Viral markers for hepatitis A virus, HBV, hepatitis C virus, hepatitis D virus, hepatitis E virus, and human immunodeficiency virus were evaluated when hepatitis occurred. Results of vital signs, physical examination, and laboratory studies were documented at each follow-up visit. The toxicity grade of each adverse event or serious adverse event was assessed according to the National Cancer Institute’s common toxicity criteria for adverse events.

The HBV DNA level, which was measured by real-time viral polymerase chain reaction (PCR) assays using the 7500 Real-Time PCR system (Applied Biosystems) with the diagnostic kit for quantification of HBV DNA (Da An Gene Co Ltd of Sun Yat-sen University) with a lower limit of 100 copies/mL, was monitored before each chemotherapy cycle, every month for 6 months after completion of chemotherapy, every 3 months for the first 1.5 years after withdrawal of antiviral prophylaxis, and every 6 months for 3 years.

End Points
The primary efficacy end point was the incidence of HBV-related hepatitis. Secondary end points included HBV reactivation frequency and chemotherapy disruption due to hepatitis. Hepatitis was defined as a ≥3-fold or greater increase in the serum ALT level that exceeded the reference range (≥8 U/L; to convert to μkat/L, divide by 0.0167) or an absolute increase in the level of ALT of greater than 100 U/L compared with the baseline level. Reactivation of HBV was defined as a ≥10-fold or greater increase in the HBV DNA level or an absolute increase of ≥10^5 copies/mL compared with the baseline value. Hepatitis related to HBV was defined as reactivation preceding or accompanying hepatitis during and after chemotherapy in the absence of clinical or laboratory features of acute infection with other hepatitis viruses or systemic disease. Chemotherapy disruption was defined as either premature termination or a delay of at least 7 days between chemotherapy cycles. Delayed HBV-related hepatitis was defined as hepatitis related to HBV reactivation (a ≥10-fold increase in the HBV DNA level or an absolute increase of ≥10^5 copies/mL compared with the baseline value) occurring more than 6 months after the initiation of chemotherapy.

Hepatitis severity was defined according to the National Cancer Institute’s common toxicity criteria for adverse events: grade 1, increase in ALT of ≥2.5 U/L or less × the upper limit of normal (ULN); grade 2, ALT between greater than 2.5 U/L × the ULN and 5 U/L or less × the ULN; grade 3, between ALT of greater than 5 U/L × the ULN and 20 U/L or less × the ULN; and grade 4, ALT of greater than 20 U/L × the ULN.

Statistical Analysis
The data were analyzed on an intention-to-treat basis. All randomized patients whose intervention was discontinued or crossed over to the other intervention were included in the analysis. Patients who were lost to follow-up were excluded from the analysis. Of the 121 patients, 4 (3.3%) missed a visit during the follow-up period. For missing blood test values, including liver function tests and HBV DNA levels, the missing value was considered normal if there were no significant symptoms reported during a telephone follow-up and if the sequential laboratory data were within the normal range or vice versa. Similarly, if the initial laboratory data were within the normal range but the subsequent data after a data gap became abnormal, then the gap data were considered abnormal without relation to the clinical status of the patients.

The sample size was calculated based on the primary end point, the incidence of HBV-related hepatitis, which was approximately 25% in a previous study of patients seropositive for the hepatitis B surface antigen. The sample size was calculated to provide 80% statistical power and a 2-sided significance level of 5%.

The Pearson χ² or Fisher exact test was used to investigate the relationships between categorical variables. Bivariable and multivariable analyses were performed to assess the association of pretreatment factors with HBV reactivation and HBV-related hepatitis, including antiviral prophylaxis with lamivudine or entecavir, sex, age, Ann Arbor stage of diffuse large B-cell lymphoma, International Prognostic Index, hepatitis B e antigen status, hepatic cirrhosis, liver involvement, R-CHOP chemotherapy cycles (≤6 vs >6), and chemotherapy interval (R-CHOP-14 vs R-CHOP-21). Factors that were significant (P < .05) or close to significant (P ≤ .10) in the bivariable analysis were included in the multivariable analysis using a generalized linear mixed model in which the site was set as level 2 and the patient was set as level 1. The covariance parameter estimate was 0, which indicated that clustering within the site was low. An interaction term (antiviral prophylaxis factor × chemotherapy interval factor) was also included in the model. A 2-tailed P ≤ .05 was considered significant. Statistical analyses were performed by investigators at the Cancer Center of Sun Yat-sen University using SPSS software version 16.0 (SPSS Inc) and SAS version 9.2 (SAS Institute Inc).
Results

A total of 534 patients newly diagnosed with diffuse large B-cell lymphoma were enrolled in the parent study, with 268 assigned to the R-CHOP-21 group and 266 assigned to the R-CHOP-14 group. There was no significant difference between the R-CHOP-21 and R-CHOP-14 groups in terms of overall response rate, 3-year overall survival rate, or 3-year progression-free survival rate. Of the 534 patients enrolled in the parent study, 229 were seropositive for the hepatitis B surface antigen and were screened for the substudy. Of these 229 patients, 108 were excluded due to liver dysfunction, high HBV DNA levels, or both (n = 55), previous use of antiviral therapy (n = 48), or refusal to participate in the study (n = 5). Therefore, 121 patients (61 in the entecavir group and 60 in the lamivudine group) were available for the intention-to-treat analyses. The Figure shows the flow of patients in the study. The median number of enrolled patients at each center was 8 (range, 6-51 patients; interquartile range, 2 patients). Twenty-nine of the 60 patients in the lamivudine group received R-CHOP-14, and the other 31 patients received R-CHOP-21. In the entecavir group, 29 of the 61 patients received R-CHOP-14, and the other 32 patients received R-CHOP-21. The median follow-up was 40.7 months (range, 8.6-62.3 months). The date of last patient follow-up was May 25, 2013.

Patient Characteristics

The baseline characteristics of the participants in the 2 groups, including sex, age, Ann Arbor stage, International Prognostic Index, status of liver involvement and cirrhosis, seropositive status for hepatitis B e antigen and hepatitis B core antibody, number of R-CHOP cycles, and the percentage who received R-CHOP-21 vs R-CHOP-14, are summarized in Table 1.

Lamivudine Group

All patients completed the protocol treatment for diffuse large B-cell lymphoma. The patients received a median of 6 cycles (range, 3-8 cycles) of R-CHOP. Forty-eight patients completed the prophylactic antiviral therapy protocol, and 12 patients received a modified antiviral treatment because of HBV-related hepatitis or HBV reactivation. The median duration of lamivudine treatment was 9.8 months (range, 1.7-19.9 months).

Among the 60 patients, 18 (30%) had HBV reactivation, and 14 (23.3%) developed hepatitis. Eight of these 14 patients were
dianosed with HBV-related hepatitis. The other 6 cases were attributed to the chemotherapy agents. Delayed hepatitis occurred in 5 patients (8.3%). Eleven patients (18.3%) experienced chemotherapy disruption, including 1 patient who terminated treatment prematurely.

For the 18 patients with HBV reactivation, the median time for occurrence after chemotherapy initiation was 5.7 months (range, 0.9-19 months). All 10 patients who developed HBV reactivation during chemotherapy and 2 of the 3 patients who developed HBV reactivation within 6 months after completion of chemotherapy received a modified antiviral treatment, including a switch to entecavir and the addition of adefovir dipivoxil. Of the 5 patients who developed HBV reactivation after the withdrawal of lamivudine, 3 received entecavir treatment, and 1 resumed treatment with lamivudine.

Of the 18 patients with HBV reactivation, 8 were diagnosed with HBV-related hepatitis. Antiviral treatment was modified for 5 patients who developed hepatitis before the withdrawal of prophylactic lamivudine, including 2 patients who were switched to entecavir, 2 who were switched to lamivudine in combination with adefovir dipivoxil, and 1 who was switched to entecavir in combination with adefovir dipivoxil. All 5 patients recovered from hepatitis. Another 3 patients who developed hepatitis after lamivudine withdrawal received entecavir treatment, and 1 died of progressive hepatic failure. The details and outcomes of the 8 patients with HBV-related hepatitis are listed in Table 2.

**Entecavir Group**

All patients completed the treatment protocol for diffuse large B-cell lymphoma. The patients received a median of 6 cycles (range, 3-8 cycles) of R-CHOP. Fifty-nine patients completed the prophylactic antiviral therapy protocol, and 2 patients received a modified antiviral treatment due to HBV reactivation. The median duration of entecavir treatment was 9.9 months (range, 7.6-14.1 months).

Among the 61 patients, 5 (8.2%) developed hepatitis and 4 (6.6%) experienced HBV reactivation. None of the patients were diagnosed with HBV-related hepatitis. All 5 cases of hepatitis were attributed to the chemotherapy drugs. One patient (1.6%) experienced chemotherapy disruption with a delay in treatment schedule. None of the patients died from HBV-related hepatitis or hepatic failure.

For the 4 patients with HBV reactivation, the median time to occurrence after the initiation of chemotherapy was 3.2 months (range, 2.3-5.2 months). The antiviral treatment was not modified for the 2 patients who exhibited a brief increase in HBV DNA level. For the 2 patients who exhibited progressively increasing HBV DNA levels, entecavir was increased to 1 mg daily, and adefovir dipivoxil was added to the antiviral treatment regimen.

**Efficacy Comparison of the 2 Groups**

The rates were significantly lower for the entecavir group vs the lamivudine group for hepatitis (8.2% vs 23.3%, respectively; difference between the 2 groups, 15.1% [95% CI, 2.4%-27.8%]; P = .02), HBV-related hepatitis (0% vs 13.3%; difference, 13.3% [95% CI, 4.7%-21.9%]; P = .003), HBV reactivation (6.6% vs 30%; difference, 23.4% [95% CI, 10.2%-36.6%]; P = .001), delayed hepatitis B (0% vs 8.3%; difference, 8.3% [95% CI, 1.3%-15.3%]; P = .03), and chemotherapy disruption (1.6% vs 18.3%; difference, 16.7% [95% CI, 6.4%-27.0%]; P = .002) (Table 3). No significant differences were observed in the severity of hepatitis between the 2 groups.

**Tolerability**

Of the 61 patients in the entecavir group, 15 (24.6%) experienced treatment-related adverse events, including 6 (9.8%)
with nausea, 4 (6.6%) with dizziness, 3 (4.9%) with headache, and 2 (3.3%) with fatigue. Of the 60 patients in the lamivudine group, 18 (30.0%) experienced treatment-related adverse events, including 6 (10.0%) with nausea, 5 (8.3%) with fatigue, 4 (6.7%) with headache, and 3 (5.0%) with dizziness. All observed adverse events were grade 1 to 2 and no grade 3 or 4 adverse events occurred. There was no significant difference between the entecavir and lamivudine groups in terms of the incidence of adverse events (24.6% vs 30.0%, respectively; difference between the 2 groups, 5.4% [95% CI, −10.5% to 21.3%]; P = .50).

Factors Associated With HBV Reactivation and HBV-Related Hepatitis

There was no effect of the interaction (antiviral prophylaxis factor × chemotherapy interval factor) on HBV reactivation in the generalized linear mixed model (P = .24). In both the bivariate and multivariable analyses, entecavir prophylaxis and limited-stage disease were associated with a lower risk for HBV reactivation (Table 4). For HBV-related hepatitis, the bivariate analysis revealed that prophylactic entecavir was associated with a lower risk for HBV-related hepatitis (odds ratio, 0.05 [95% CI, 0.00-0.89]; P = .003).

Table 3. Efficacy Comparison of the Lamivudine and Entecavir Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of Patients</th>
<th>Entecavir (n = 61)</th>
<th>Lamivudine (n = 60)</th>
<th>Difference Between Groups, % (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hepatitis</td>
<td>5 (8.2)</td>
<td>14 (23.3)</td>
<td>15.1 (2.4-27.8)</td>
<td>0.29 (0.10-0.88)</td>
<td>.02*</td>
<td></td>
</tr>
<tr>
<td>Severity of hepatitisb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (3.3)</td>
<td>3 (5.0)</td>
<td>0.7 (−0.6 to 2.1)</td>
<td>.58*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>4 (6.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (4.9)</td>
<td>5 (8.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (3.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>4 (6.6)</td>
<td>18 (30.0)</td>
<td>23.4 (10.2-36.6)</td>
<td>0.16 (0.05-0.52)</td>
<td>.001*</td>
<td></td>
</tr>
<tr>
<td>HBV-related hepatitis</td>
<td>0</td>
<td>8 (13.3)</td>
<td>13.3 (4.7-21.9)</td>
<td>0.05 (0.003-0.89)</td>
<td>.03*</td>
<td></td>
</tr>
<tr>
<td>Delayed hepatitis B</td>
<td>0</td>
<td>5 (8.3)</td>
<td>8.3 (1.3-15.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy disruption</td>
<td>1 (1.6)</td>
<td>11 (18.3)</td>
<td>16.7 (6.4-27.0)</td>
<td>0.07 (0.01-0.60)</td>
<td>.002*</td>
<td></td>
</tr>
<tr>
<td>Premature termination</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay ≥7 d</td>
<td>1 (1.6)</td>
<td>10 (16.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HBV, hepatitis B virus.
* Determined using the χ² test.
b Grade 1 indicates an increase in alanine aminotransferase (ALT) of 2.5 U/L or less × the upper limit of normal (ULN); grade 2, ALT between greater than 2.5 U/L × the ULN and 5 U/L or less × the ULN; grade 3, ALT between greater than 5 U/L × the ULN and 20 U/L or less × the ULN; grade 4, ALT of greater than 20 U/L × the ULN.14

Table 2. Details and Outcome of 8 Patients With Hepatitis Related to Hepatitis B Virus (HBV) in the Lamivudine Group

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Ann Arbor Stage</th>
<th>Ann Arbor IPI</th>
<th>HBeAg Status at Baseline</th>
<th>No. of Cycles of R-CHOP Before Hepatitis</th>
<th>No. of Days After Last Cycle of R-CHOP</th>
<th>HBV DNA, copies/mL</th>
<th>HBV reactivation</th>
<th>Antiviral Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>IV</td>
<td>2</td>
<td>Seropositive</td>
<td>4</td>
<td>187</td>
<td>4.76 × 10⁷</td>
<td>Seropositive</td>
<td>Switched to entecavir</td>
<td>Alive with cirrhosis</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>IV</td>
<td>1</td>
<td>Seropositive</td>
<td>4</td>
<td>110</td>
<td>5.97 × 10⁵</td>
<td>Seropositive</td>
<td>Switched to entecavir</td>
<td>Alive and well</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>III</td>
<td>1</td>
<td>Seropositive</td>
<td>6</td>
<td>0b</td>
<td>3.2 × 10⁶</td>
<td>Seropositive</td>
<td>Switched to lamivudine plus adefovir dipivoxil</td>
<td>Died of lymphoma</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>F</td>
<td>IV</td>
<td>4</td>
<td>Seropositive</td>
<td>8</td>
<td>281</td>
<td>7.34 × 10⁶</td>
<td>Seropositive</td>
<td>Switched to entecavir</td>
<td>Died of liver failure</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>M</td>
<td>IV</td>
<td>2</td>
<td>Seropositive</td>
<td>7</td>
<td>0b</td>
<td>5.37 × 10⁵</td>
<td>Seropositive</td>
<td>Switched to lamivudine plus adefovir dipivoxil</td>
<td>Alive and well</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>III</td>
<td>1</td>
<td>Seronegative</td>
<td>7</td>
<td>137</td>
<td>1 × 10⁰</td>
<td>Seropositive</td>
<td>Switched to entecavir</td>
<td>Alive and well</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>M</td>
<td>IV</td>
<td>2</td>
<td>Seronegative</td>
<td>6</td>
<td>209</td>
<td>8.98 × 10⁷</td>
<td>Seropositive</td>
<td>Switched to entecavir</td>
<td>Alive and well</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>M</td>
<td>II</td>
<td>0</td>
<td>Seronegative</td>
<td>2</td>
<td>0b</td>
<td>3.12 × 10⁵</td>
<td>Seropositive</td>
<td>Switched to entecavir plus adefovir dipivoxil</td>
<td>Alive and well</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

* Levels of HBV DNA were less than 1000 copies/mL for each patient in this Table at baseline.

b Patient acquired HBV-related hepatitis during R-CHOP cycle.

Si conversion factor: To convert ALT to μkat/L, divide by 0.0167.
Discussion

Diffuse large B-cell lymphoma is the most common NHL subtype, accounting for approximately one-third of all cases.\textsuperscript{18} The CHOP regimen has been the standard of care for patients with diffuse large B-cell lymphoma for more than 25 years. The introduction of rituximab into the therapeutic regimen revolutionized the prognosis of diffuse large B-cell lymphoma,\textsuperscript{7,8,19-21} and the R-CHOP regimen has become the criterion standard, first-line treatment for the disease. Due to the high prevalence of HBV infection, ranging from 8.1% to 25% in patients with diffuse large B-cell lymphoma,\textsuperscript{22-24} HBV reactivation is common during and after chemotherapy. The use of glucocorticoids and anthracyclines has been reported as a risk factor for HBV reactivation.\textsuperscript{1,9,25}

Rituximab, a human-mouse chimeric monoclonal antibody that specifically binds to the CD20 antigen located on pre-B and mature B lymphocytes, can induce profound and durable B-cell depletion, resulting in secondary immunosuppression. Rituximab is generally well tolerated with minimal late toxicity. However, increasing evidence indicates that rituximab is associated with a high risk for HBV reactivation. Recent data suggest that the incorporation of rituximab into the standard CHOP regimen markedly increases the risk for HBV reactivation in patients with resolved HBV infection,\textsuperscript{26} which is defined as being seronegative for the hepatitis B surface antigen and seropositive for the hepatitis B core antibody, hepatitis B surface antibody, or both. A meta-analysis of patients seropositive for the hepatitis B core antibody identified a more than 5-fold increased rate of rituximab-associated HBV reactivation.\textsuperscript{27} For patients seropositive for the

Table 4. Analysis of Factors Associated With HBV Reactivation

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Bivariable</th>
<th>Multivariable\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Antiviral prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>6.11 (1.93-19.37)</td>
<td>.001</td>
</tr>
<tr>
<td>Entecavir</td>
<td>4.24 (1.44-12.40)</td>
<td>.008</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.41 (0.87-6.67)</td>
<td>.08</td>
</tr>
<tr>
<td>Female</td>
<td>0.66 (0.25-1.71)</td>
<td>.39</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>0.66 (0.25-1.71)</td>
<td>.39</td>
</tr>
<tr>
<td>&gt;40</td>
<td>3.46 (1.09-10.96)</td>
<td>.03</td>
</tr>
<tr>
<td>International Prognostic Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1.61 (0.47-5.57)</td>
<td>.68</td>
</tr>
<tr>
<td>3-5</td>
<td>9.80 (0.85-113.36)</td>
<td>.09</td>
</tr>
<tr>
<td>Seropositive</td>
<td>3.46 (1.09-10.96)</td>
<td>.03</td>
</tr>
<tr>
<td>Seronegative</td>
<td>0.66 (0.25-1.71)</td>
<td>.39</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.80 (0.85-113.36)</td>
<td>.09</td>
</tr>
<tr>
<td>No</td>
<td>0.74 (0.08-6.46)</td>
<td>.78</td>
</tr>
<tr>
<td>Cycles of R-CHOP chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>2.60 (1.00-6.78)</td>
<td>.05</td>
</tr>
<tr>
<td>&gt;6</td>
<td>0.89 (0.35-2.24)</td>
<td>.80</td>
</tr>
<tr>
<td>Chemotherapy interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 wk (R-CHOP-14)</td>
<td>0.89 (0.35-2.24)</td>
<td>.80</td>
</tr>
<tr>
<td>3 wk (R-CHOP-21)</td>
<td>1.00 (0.35-2.84)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
\textsuperscript{a} Calculated using the \chi^2 test except for hepatic cirrhosis, which was calculated using the Fisher exact test.

\textsuperscript{b} Included antiviral prophylaxis (lamivudine vs entecavir), sex (male vs female), Ann Arbor stage (stages I-II vs III-IV), hepatic cirrhosis (positive vs negative), cycles of R-CHOP chemotherapy (≤6 vs >6).

\textsuperscript{c} Calculated using the generalized linear mixed model.
hepatitis B surface antigen and with NHL who were receiving rituximab-containing chemotherapy without prophylactic antiviral therapy, the incidence of HBV reactivation ranged from 16% to 80%.27

Antiviral prophylaxis reduces the incidence of HBV reactivation, the severity of associated hepatitis, and mortality. Although studies to date have focused on lamivudine, both tenofovir and entecavir, which have been recommended as first-line therapies for chronic HBV infection,28,29 may be used as alternatives. The limited data available indicate entecavir is effective in preventing HBV reactivation during chemotherapy.30

To our knowledge, this is the first randomized clinical study comparing the prophylactic use of entecavir and lamivudine to prevent HBV reactivation during R-CHOP chemotherapy in patients seropositive for the hepatitis B surface antigen with newly diagnosed diffuse large B-cell lymphoma. In our study, entecavir prophylaxis was associated with significantly lower rates of HBV reactivation, delayed HBV-related hepatitis, and chemotherapy disruption compared with lamivudine, which is similar to the results of our previous retrospective study of lymphoma.31 However, the patients enrolled in this study and the treatment regimens were more homogenous than those in our previous study.

The better efficacy of entecavir could have resulted from its potent antiviral activity and high genetic barrier to resistance because large prospective studies32-34 have indicated that entecavir is more effective than lamivudine with respect to histological improvement, virological response, and normalization of ALT levels for both patients seropositive for the hepatitis B e antigen with respect to histological improvement, virological response, and normalization of ALT levels for both patients seropositive for the hepatitis B surface antigen with resolved hepatitis B, and the cumulative HBV reactivation rates at 6, 12, and 18 months after chemotherapy were 0%, 0%, and 4.3%, respectively. In our study, no cases of HBV reactivation occurred after the withdrawal of antiviral treatment in the entecavir group, suggesting that 6 months of prophylactic antiviral treatment after immunochemotherapy completion may not be sufficient. However, previous studies have focused on lamivudine prophylaxis.

Huang et al13 investigated 3-month entecavir prophylaxis treatment after rituximab-based chemotherapy in patients with resolved hepatitis B, and the cumulative HBV reactivation rates at 6, 12, and 18 months after chemotherapy were 0%, 0%, and 4.3%, respectively. In our study, no cases of HBV reactivation occurred after the withdrawal of antiviral treatment in the entecavir group, suggesting that 6 months of prophylactic antiviral treatment after completion of chemotherapy may be sufficient; however, this needs to be investigated further in other studies.

The National Comprehensive Cancer Network guidelines for cancer-related infections recommended 6 to 12 months of antiviral treatment after the last dose of rituximab.35 In addition, the European Association for the Study of the Liver clinical practice guidelines for the management of chronic hepatitis recommended that patients seropositive for the hepatitis B surface antigen who are candidates for immunosuppressive therapy should be administered preemptive nucleoside analog during therapy (regardless of HBV DNA levels) and for 12 months after the cessation of therapy.29 However, the optimal duration of prophylactic antiviral treatment may vary for different antiviral drugs and requires further investigation.

Entecavir and lamivudine are nucleoside analogs that suppress viral replication. In our study, the incidence of HBV reactivation was higher in the lamivudine group than in the entecavir group. Moreover, of the 18 HBV reactivation cases, 8 (44.4%) developed HBV-related hepatitis with lamivudine prophylaxis. Of 61 patients, 4 (6.6%) developed HBV reactivation...
Entecavir vs Lamivudine to Prevent HBV

Original Investigation Research

entecavir prophylaxis. Of the remaining 10 patients with HBV reactivation but without hepatitis flares in the lamivudine group, 7 received a modified antiviral therapy, and their increased HBV DNA levels gradually declined.

Because entecavir is more expensive than lamivudine, further studies are needed to determine whether all patients seropositive for the hepatitis B surface antigen who receive rituximab-based immunosuppressive therapy should be given entecavir to prevent HBV flares and to determine which patients will benefit most from entecavir prophylaxis. Antiviral prophylaxis and Ann Arbor stage had a significant effect on HBV reactivation. Prophylactic entecavir reduced the risk of HBV reactivation and HBV-related hepatitis. Patients with advanced-stage disease had a higher risk for HBV reactivation, possibly because these patients received more cycles of chemotherapy and had a poorer performance status.

A limitation of this study is that genotypic resistance mutations in patients with HBV reactivation were not examined.

The incidence of lamivudine drug resistance after 1 year is as high as 30%. Whether the HBV reactivation observed in the lamivudine group was associated with resistant mutations is unclear.

Other limitations include the relatively small sample sizes and small numbers of outcomes, and this warrants further investigation before definitive conclusions about efficacy should be made.

Conclusions

Among patients seropositive for the hepatitis B surface antigen with diffuse large B-cell lymphoma undergoing R-CHOP chemotherapy, the addition of entecavir compared with lamivudine resulted in a lower incidence of HBV-related hepatitis and HBV reactivation. If replicated, these findings support the use of entecavir in these patients.

ARTICLE INFORMATION

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Author Contributions: Dr. T. Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Huang, Liu, T. Lin. Acquisition, analysis, or interpretation of data: All authors.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by a grant from the Foundation of 5010 Clinical Trials of Sun Yat-sen University.

Role of the Funder/Sponsor: The Foundation of 5010 Clinical Trials of Sun Yat-sen University had full administrative responsibility but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the patients and their families for participation in the study. We are grateful to all medical staff, staff nurses, and research nurses at the 10 medical centers, all of whom strongly contributed to the success of the study.

REFERENCES


