HEPATITIS B REACTIVATION AFTER WITHDRAWAL OF PREEMPTIVE LAMIVUDINE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCY UPON COMPLETION OF CYTOTOXIC CHEMOTHERAPY

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Abbreviations: HBV- hepatitis B virus, HBsAg- hepatitis B surface antigen, HBeAg- hepatitis B e antigen, anti-HBe- hepatitis B e antibody, RR- relative risk, 95%CI- 95% confidence interval, ALT- alanine aminotransaminase

Keywords: Preemptive lamivudine, chemotherapy, HBV reactivation, hepatic failure, withdrawal of lamivudine

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Abstract.

**Background:** The hepatic outcome of hepatitis B surface antigen (HBsAg)-positive patients undergoing chemotherapy after withdrawal of preemptive lamivudine is unknown.

**Aims:** To examine the occurrence of hepatitis B virus (HBV) reactivation after withdrawal of preemptive lamivudine.

**Methods:** Preemptive lamivudine was started 1 week before initiation of chemotherapy in 46 consecutive HBsAg-positive patients and continued for the entire duration of chemotherapy. Preemptive lamivudine was stopped at a median 3.1 (range 3.0-3.4) months after completion of chemotherapy. Patients were longitudinally followed-up after withdrawal of preemptive lamivudine.

**Results:** The median time of follow-up after withdrawal of lamivudine was 25.7 (range 5.7-75.7) months. Eleven of the 46 patients (23.9%) developed HBV reactivation after withdrawal of preemptive lamivudine. Eight of the 16 patients with high prechemotherapy HBV DNA (>10^4 copies/ml) compared with 3 of the 30 patients with low prechemotherapy HBV DNA (<10^4 copies/ml) developed HBV reactivation (50.0% vs. 10.0% respectively, p<0.001). Hepatitis B e antigen-positive patients were also more likely to develop HBV reactivation [5 of 11 (45.5%) vs. 6 of 35 (17.1%) respectively, p=0.041]. A high prechemotherapy HBV DNA (>10^4 copies/ml) was the most important risk factor for HBV reactivation after withdrawal of preemptive lamivudine on Cox proportional hazards analysis [Relative Risk 16.13, 95%Confidence Interval 2.99-87.01, p=0.001].

**Conclusions:** HBV reactivation is more likely to occur in patients with high prechemotherapy HBV DNA after withdrawal of preemptive lamivudine. A more prolonged course of antiviral therapy may be necessary in these patients after completion of chemotherapy in order to reduce post-chemotherapy HBV reactivation.
INTRODUCTION

Hepatitis due to hepatitis B virus (HBV) reactivation is a serious cause of liver related morbidity and mortality in hepatitis B surface antigen (HBsAg) positive patients undergoing cytotoxic or immunosuppressive therapy.[1][2] Liver damage due to HBV reactivation is a two-stage process. Initially during intense cytotoxic or immunosuppressive therapy, there is an increase in viral replication as reflected by an increase in the serum level of HBV DNA, hepatitis B e antigen (HBeAg) and HBV DNA polymerase resulting in widespread infection of hepatocytes. The restoration of immune function due to the withdrawal of cytotoxic or immunosuppressive therapy will then result in a rapid immune mediated destruction of HBV infected hepatocytes. This destruction of HBV infected hepatocytes can manifest as hepatitis, hepatic failure and even death.[2][3][4]

Although initial reports of HBV reactivation involved mainly patients with hematological malignancies, it has also been reported in patients with solid tumors.[3][5][6][7][8][9] Reactivation of HBV replication with decompensation has been reported in 20-50% of chronic HBV patients undergoing cytotoxic chemotherapy. [3] [8][10] With the increasing incidence of neoplastic diseases and more widespread use of cytotoxic chemotherapy, the incidence of HBV reactivation is likely to rise further in HBV endemic areas and in migrants from HBV endemic areas.[11] This has lead to the recent recommendation that patients undergoing cytotoxic chemotherapy should be screened for HBsAg before initiation of chemotherapy. [12]

Since HBV reactivation due to cytotoxic or immunosuppressive therapy is related to the host immune response to enhanced HBV replication, antiviral agents such as lamivudine or famciclovir has been used to decrease the risk of HBV reactivation in patients receiving immunosuppressive therapy.[13][14][15][16][17][18] However, despite the use of nucleoside analogues at the time of clinical hepatitis, hepatic failure and mortality still occurred. This is likely to be due to the late institution of nucleoside analogues when the immune mediated damage of the liver has already been established.[19] Hence, it is accepted that nucleoside analogues should be administered preemptively before the onset of clinical hepatitis due to HBV virological reactivation.[19][20][21]

The availability of data on the safety and efficacy of lamivudine as preemptive therapy for patients undergoing cytotoxic or immunosuppressive therapy has led to a consensus recommendation that all patients with chronic HBV infection should be given a short course of lamivudine while receiving cytotoxic or immunosuppressive therapy as prophylaxis against reactivation of HBV.[12][22] But, as prolonged lamivudine therapy is associated with an increased likelihood of developing lamivudine resistant mutants, most cancer centers would aim at discontinuing or withdrawing preemptive lamivudine as soon as possible in order to limit the duration of antiviral therapy.[20][21][23][24][25][26] However, at the moment there is no available consensus on the optimal duration of lamivudine therapy. This is mostly due to the lack of data on the occurrence of hepatic flares after the withdrawal of preemptive antiviral therapy in these patients.

The current recommendation is for prophylactic lamivudine to be started 1 week before and continued for at least 6 weeks after the end of chemotherapy in order to reduce the frequency and severity of HBV reactivation.[12] Based on reported series, the continuation of lamivudine for a variable period of 1 to 6 months after completion of
chemotherapy has been shown to be equally effective in reducing HBV reactivation.[13] [16][17][27][28] However, the duration of preemptive lamivudine in these studies is arbitrary and a predetermined set of criteria for the withdrawal of lamivudine after the completion of chemotherapy is not employed.

As HBV reactivation after cytotoxic or immunosuppressive therapy is usually accompanied by an upsurge of white cell counts from the nadir, our Centre has adopted a protocol of only withdrawing lamivudine once the total white cell count has normalized (more than 4.0 X 10^9/L) and at least 3 months after completion of chemotherapy.[21] The concept of this protocol or approach is to cover the entire period when the host interaction with HBV has been disturbed as a result of the cytotoxic or immunosuppressive therapy. This way, we would only be withdrawing lamivudine after recovery from the effects of cytotoxic or immunosuppressive therapy and at a time when the host’s immune system have recovered sufficiently to the prechemotherapy state.

In our present study, we examined the occurrence of hepatic flares after withdrawal of preemptive lamivudine, and to determine what factors are associated with hepatic flares after withdrawal of preemptive lamivudine.

PATIENTS AND METHODS
Patients studied.

From 1999 to December 2004, 1093 consecutive patients were treated with intravenous cytotoxic chemotherapy for hematological malignancy at the Hematology and Oncology Unit, University Department of Medicine, Queen Mary Hospital, Hong Kong SAR, China. All the patients were screened for HBsAg, hepatitis B surface antibody (anti-HBs) (enzyme-linked immunosorbent assay II; Abbott Laboratories, Chicago, IL, USA), human immunodeficiency virus antibody (Abbott Laboratories, Chicago, IL, USA) and hepatitis C virus antibody (Ortho Diagnostics System, Raritan, NJ, USA). Further testing for HBeAg, hepatitis B e antibody (anti-HBe) [Abbott Laboratories, Chicago, IL, USA] and serum HBV DNA was performed on all HBsAg positive patients. Serum HBV DNA was quantified by real time PCR using the DyNAtoTM HS SYBR® Green qPCR kit (Finnzymes Oy, Finland) as previously described by our group.[29] The linear quantification range of our assay is 10^2 to 10^8 copies/ml.

All HBsAg positive patients were assessed by an experienced hepatologist (GKKL) before initiation of chemotherapy. None of the HBsAg positive patients had clinical evidence of decompensated cirrhosis (ankle edema, ascites, jaundice, and hepatic encephalopathy), and their albumin, bilirubin, and prothrombin time were all within normal range.

All HBsAg positive patients were managed by a single hepatologist (GKKL) according to a standardized protocol. Preemptive lamivudine was started one week before initiation of chemotherapy. Preemptive lamivudine was continued throughout the entire period of chemotherapy and was discontinued at least 3 months after the completion of chemotherapy and when the total white cell count had normalized (normal range 4.0-11.0 X 10^9/L).

All patients were prospectively followed up every two weeks while on lamivudine or chemotherapy. After the withdrawal of lamivudine, the patients were prospectively followed up every two weeks for the first three months and then monthly until the time of
analysis (March 2005) or death. At each follow up visit, the clinical status of the recipients was recorded and blood was tested for liver biochemistry [serum alanine aminotransaminase (ALT), aspartate aminotransaminase, bilirubin and albumin]. HBsAg, HBeAg, anti-HBs and anti-HBe and serum HBV DNA were also tested on every visit.

Patients developing hepatic failure were tested for lamivudine resistant mutants by determination of HBV polymerase gene by direct sequencing as previously described.[15]

Definition of hepatic events

HBV-related hepatitis during chemotherapy was diagnosed in the presence of a more than three-fold elevation of serum ALT levels on two consecutive tests five days apart accompanied by an elevation of serum HBV DNA to more than 10 times that of the pre-exacerbation baseline in a patient who remained HBV DNA positive or if the serum HBV DNA turned from negative to positive.

HBV reactivation after lamivudine withdrawal was defined as elevation of serum ALT levels above the upper limit of normal, on two consecutive determinations at least five days apart accompanied by a serum HBV DNA more than \(10^5\) copies/ml in HBeAg positive patients or elevated serum ALT levels on two consecutive determinations five days apart accompanied by a serum HBV DNA of more than \(10^5\) copies/ml in HBeAg negative patients.[22] Hepatic failure was defined as the presence of hepatic encephalopathy and deranged blood coagulation (prothrombin time exceeding 10 seconds of control).

This study was approved by the Institutional Review Board of the Queen Mary Hospital, Hong Kong SAR, China. Informed consent was obtained from all patients for longitudinal follow-up.

Statistical Analysis.

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 12.5 for windows; SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used for comparing two continuous variables and the chi-square with Yates’ correction for continuity or Fisher’s exact test was used for comparing two categorical variables. The primary outcome measure was the occurrence of HBV reactivation after withdrawal of lamivudine. The secondary outcome measure was to determine the occurrence of hepatic failure due to HBV reactivation after withdrawal of lamivudine and to determine the variables associated with HBV reactivation and hepatic failure after lamivudine withdrawal. The Kaplan-Meier method was employed for calculation of the cumulative probability of HBV reactivation. A Cox’s proportional hazards model was used to estimate the relative risk (RR) of HBV reactivation after withdrawal of lamivudine and hepatic failure associated with HBV DNA more than \(10^4\) copies/ml, positive HBeAg and abnormal serum ALT levels prechemotherapy. The 95% confidence interval (CI) for the RR was also calculated. Continuous variables were expressed as median (range). All statistical analyses were performed on an intention-to-treat basis. Statistical significance was defined as \(p<0.05\) (2 tailed).
RESULTS

One hundred and twenty eight of the 1093 patients (11.7%) were HBsAg positive. Of these 128 HBsAg positive patients, 82 were excluded from the analysis for the following reasons; 41 (32.0%) patients had hematopoietic stem cell transplantation after clinical remission was achieved, 30 (23.4%) patients have already been included into a previous study [21], 9 (7.0%) patients died of disease progression and were still on lamivudine at the time of fatality and 2 (1.6%) patients developed YMDD resistance while on lamivudine and were commenced on adefovir dipivoxil in addition to lamivudine. None of these 46 patients had stigmata of chronic liver disease or evidence of liver cirrhosis before chemotherapy. The remaining 46 of these of 128 patients (35.9%) were included into this study. The demographic data of these 46 patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; M: F</td>
<td>23:23</td>
</tr>
<tr>
<td>Age, years</td>
<td>46 (21-78)</td>
</tr>
<tr>
<td>Alanine aminotransaminase, U/L</td>
<td>27 (10-108)</td>
</tr>
<tr>
<td>Elevated alanine aminotransaminase:</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>42</td>
</tr>
<tr>
<td>HBV DNA more than $10^4$ copies/ml:</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>No</td>
<td>30</td>
</tr>
<tr>
<td>Hepatitis B e Antigen:</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11</td>
</tr>
<tr>
<td>Negative</td>
<td>35</td>
</tr>
<tr>
<td>Hepatitis B e antibody:</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>35</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>33</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>8</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3</td>
</tr>
<tr>
<td>Chemotherapy regimen:</td>
<td></td>
</tr>
<tr>
<td>Use of steroid containing chemotherapy</td>
<td>36</td>
</tr>
<tr>
<td>Use of anthracycline containing chemotherapy</td>
<td>35</td>
</tr>
<tr>
<td>Use of vinca alkaloid containing chemotherapy</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 1. Prechemotherapy clinical and virologic characteristics of the 46 patients included into the study. Continuous variables expressed in median (range). Alanine aminotransaminase (normal range 13-51 U/L).
None of these 46 patients developed HBV-related hepatitis during the course of chemotherapy. The median duration of preemptive lamivudine in conjunction with chemotherapy is shown in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Median duration (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of lamivudine before chemotherapy</td>
<td>1.0 (0.9-2.0) week</td>
</tr>
<tr>
<td>Duration of lamivudine during chemotherapy</td>
<td>5.9 (3.0-27.6) months</td>
</tr>
<tr>
<td>Duration between end of chemotherapy and withdrawal of lamivudine</td>
<td>3.1 (3.0-3.4) months</td>
</tr>
<tr>
<td>Total duration of preemptive lamivudine</td>
<td>9.2 (6.2-31.5) months</td>
</tr>
</tbody>
</table>

Table 2. The median time of from initiation of preemptive lamivudine to withdrawal of lamivudine in conjunction with chemotherapy.

**HBV Reactivation After Withdrawal of Preemptive Lamivudine**

The median time of follow-up after the withdrawal of lamivudine to the time of analysis in these 46 patients was 25.7 (range 5.7-75.7) months. At the time of withdrawal, all patients (100%) had a serum HBV DNA level of less than $10^4$ copies/ml.

Eleven of the 46 patients (23.9%) developed HBV reactivation after withdrawal of lamivudine [Figure 1]. The cumulative probability of HBV reactivation after lamivudine withdrawal at 3, 6, 12, 18, 24 and 36 months were 0%, 2%, 5%, 13%, 16% and 33% respectively [Figure 1]. Lamivudine was resumed in all 11 patients who developed HBV reactivation. The baseline characteristics of patients with and without HBV reactivation after withdrawal of lamivudine are shown in Table 3.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with HBV reactivation after withdrawal of lamivudine (n=11)</th>
<th>Patients without HBV reactivation after withdrawal of lamivudine (n=35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; M: F</td>
<td>7:4</td>
<td>16:19</td>
<td>0.491</td>
</tr>
<tr>
<td>Age, years</td>
<td>51 (24-71)</td>
<td>44 (21-78)</td>
<td>0.787</td>
</tr>
<tr>
<td>Alanine aminotransaminase, U/L</td>
<td>21 (12-55)</td>
<td>28 (10-108)</td>
<td>0.523</td>
</tr>
<tr>
<td>Elevated alanine aminotransaminase:</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>HBV DNA more than 10^4 copies/ml:</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B e Antigen:</td>
<td></td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Positive</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td>0.689</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>8</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Duration of lamivudine, months</td>
<td>11.8 (7.3-29.3)</td>
<td>7.8 (7.2-31.5)</td>
<td>0.634</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of patients with and without HBV reactivation after withdrawal of lamivudine. Continuous variables expressed in median (range). Alanine aminotransaminase (normal range 13-51 U/L).

Factors predictive of HBV reactivation after withdrawal of lamivudine were a serum HBV DNA of more than 10^4 copies/ml before chemotherapy [8 of 16 patients (50.0%) vs. 3 of 30 patients (10.0%) respectively, p<0.001 on log rank][Figure 2A] and a positive HBeAg before chemotherapy [5 of 11 patients (45.5%) vs. 6 of 35 patients (17.1%) respectively, p=0.041 on log rank] [Figure 2B].

When multivariate Cox regression analysis was used to assess HBV reactivation after withdrawal of preemptive lamivudine, a serum HBV DNA of more than 10^4 copies/ml before chemotherapy was the only independent factor in predicting HBV reactivation after withdrawal of preemptive lamivudine (RR 16.13, 95%CI 2.99-87.01, p=0.001) [Table 4].
<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted relative risk (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &gt; 10^4 copies/ml prechemotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16.13 (2.99-87.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HBeAg prechemotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.39 (0.38-5.11)</td>
<td>0.621</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abnormal serum alanine aminotransaminase prechemotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.596 (0.07-5.04)</td>
<td>0.635</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Adjusted relative risk of HBV reactivation after withdrawal of lamivudine according to various risk factors. 
HBV- hepatitis B virus, HBeAg- hepatitis B e antigen, CI- confidence interval
Alanine aminotransaminase (normal range 13-51 U/L).

**Hepatic Failure due to HBV Reactivation After Withdrawal of Lamivudine**

Three of the 11 patients (27.3%) with HBV reactivation after withdrawal of lamivudine developed fulminant hepatic failure. None of these 3 patients with hepatic failure had lamivudine resistant mutants. The characteristics of these 3 patients are shown in Table 5 (Figure 3).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>HBV status before chemotherapy</th>
<th>Time of HBV reactivation after initiation of chemotherapy</th>
<th>Time of HBV reactivation after lamivudine withdrawal</th>
<th>HBV DNA &gt; 10^4 copies/ml before chemotherapy</th>
<th>Elevated ALT before chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>M</td>
<td>+</td>
<td>16.0</td>
<td>7.6</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>M</td>
<td>+</td>
<td>17.8</td>
<td>5.8</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>+</td>
<td>24.7</td>
<td>13.8</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 5. Clinical characteristics of the 3 patients with hepatic failure due to HBV reactivation after withdrawal of lamivudine. 
HBV- hepatitis B virus, HBsAg- hepatitis B surface antigen, HBeAg- hepatitis B e antigen, anti-HBe- hepatitis B e antibody, ALT- alanine aminotransaminase. 
Alanine aminotransaminase (normal range 13-51 U/L).
One of these 11 patients (9.1%) died from bleeding esophageal varices and hepatic encephalopathy. Ten of 11 patients (90.9%) with HBV reactivation recovered with lamivudine therapy. All 10 patients were still alive at the time of analysis.

Hepatic failure was higher in patients with a serum HBV DNA of more than $10^4$ copies/ml before chemotherapy [3 of the 16 patients (18.8%) vs. none of the 30 patients (0%) respectively, $p=0.005$ on log rank]. Two of the 11 HBeAg positive patients compared with 1 of the 35 HBeAg negative patients developed hepatic failure after withdrawal of lamivudine (18.2% vs. 2.9% respectively, $p=0.069$ on log rank). One of the 4 patients with elevated serum ALT levels before chemotherapy compared with 2 of the 42 patients without elevated serum ALT levels before chemotherapy developed hepatic failure after withdrawal of lamivudine (25.0% vs. 4.8% respectively, $p=0.068$ on log rank).

The relative risk of developing hepatic failure after withdrawal of lamivudine was higher in patients with serum HBV DNA of more than $10^4$ copies/ml before chemotherapy and in patients with positive HBeAg before chemotherapy [Table 6].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted relative risk (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA $&gt;10^4$ copies/ml prechemotherapy:</td>
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<td>0.345</td>
</tr>
<tr>
<td>Yes</td>
<td>17.82 (0.56-35.78)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HBeAg prechemotherapy:</td>
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</tr>
<tr>
<td>Positive</td>
<td>1.85 (0.17-20.53)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
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<td></td>
</tr>
<tr>
<td>Elevated serum alanine aminotransaminase prechemotherapy:</td>
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<td>0.746</td>
</tr>
<tr>
<td>Yes</td>
<td>1.49 (0.13-16.87)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Adjusted relative risk of hepatic failure due to HBV reactivation after withdrawal of lamivudine according to various factors.

CI- confidence interval

Alanine aminotransaminase (normal range 13-51 U/L).

**HBV Serology**

None of the 11 HBeAg positive (0%) patients lost HBeAg while none of the 35 anti-HBe positive (0%) patients developed HBeAg reversion after withdrawal of lamivudine.

**DISCUSSION**

Nucleoside analogues such as lamivudine or adefovir dipivoxil are now available for the treatment of hepatitis due to HBV reactivation in HBsAg positive subjects undergoing intense chemotherapy. With the results from recent studies, it is now generally accepted that early rather than deferred preemptive therapy with these anti-viral
agents should be adopted for HBsAg lymphoma patients undergoing intense chemotherapy to reduce post chemotherapy HBV related morbidity and mortality.[21][30] However, the optimal duration of lamivudine administration has not yet been defined. An additional 1-6 months administration of lamivudine after completion of chemotherapy has been recommended by some studies.[13][16][17][27][28] Nevertheless, prolonged use of lamivudine cannot guarantee its clinical benefit due to the emergence of lamivudine resistant strains at 10-30% after one year of therapy.[31] On the other hand, if the duration of lamivudine therapy is too short, there is a risk that the antiviral prophylaxis may not be adequate.

One of the major concerns with the use of lamivudine has been the occurrence of withdrawal hepatic flares on stopping lamivudine.[32] A few studies have reported follow-up of patients with preemptive lamivudine being withdrawn 1-6 months after the completion of chemotherapy. One reported no incidence of post-lamivudine hepatitis flare in its 3 cases,[27] the other had one case of hepatic flare among 20 patients [28] while the third only reported hepatic flares in 4 of their 65 patients.[20] The hepatic flares in these studies were all reported to be self-limiting. However, the follow-up period after the withdrawal of lamivudine was short and limited to around 8-12 weeks after the withdrawal of preemptive lamivudine. One recent publication however, reported delayed HBV reactivation in 4 HBsAg positive lymphoma patients at 6-8 months after withdrawal of lamivudine.[30] Furthermore, there has been report on cases of hepatic failure resulting in fatality after the withdrawal of lamivudine in immunocompetent patients with chronic HBV.[33]

In this study we have longitudinally followed-up a cohort of patients on preemptive lamivudine for a median of 25.7 (range 6-75) months. All the patients had their preemptive lamivudine withdrawn under the same set of criteria. At the time of analysis, the cumulative probability of HBV reactivation 36 months after withdrawal of lamivudine was 33%. The occurrence of hepatic flares due to HBV reactivation in this series is not as benign or as self-limiting as previously reported.[20] In fact, 3 patients developed hepatic failure, with one fatality. The 3 cases of hepatic failure developed within 13 months of lamivudine withdrawal. None of these 3 patients with hepatic failure had lamivudine resistant mutants detected on direct PCR sequencing. Thus, patients should be monitored closely for a more prolonged period of time since no patient developed HBV reactivation within the first 3 months after lamivudine withdrawal [Figure 1].

A serum HBV DNA more than $10^4$ copies/ml before chemotherapy is an independent risk factor for the development of HBV reactivation after the withdrawal of preemptive lamivudine. The withdrawal of lamivudine would result in a “rebound” and resurgence of the viral replication.[32] This “rebound” can result in the HBV DNA returning to its prechemotherapy level or even higher as shown in Figure 3 and is in keeping with the observation made in other study [30]. This explains why patients with a higher prechemotherapy HBV DNA have a higher risk of developing HBV reactivation or even hepatic failure after withdrawal of lamivudine.

In this study, HBeAg positive patients had a higher risk of developing HBV reactivation after the withdrawal of preemptive lamivudine. This is probably because HBeAg positive patients have a higher HBV DNA level despite a normal serum ALT level (the immune-tolerant phase).[4][22] Furthermore, patients in the immune-tolerant
phase are also less likely to develop HBeAg seroconversion despite lamivudine, explaining why none of the 11 HBeAg positive patients in this study developed HBeAg seroconversion while on lamivudine.[34]

Therefore, patients with a high prechemotherapy serum HBV DNA might need a prolonged course of lamivudine in order to maintain remission of HBV. HBeAg positive patients might even require HBeAg seroconversion before preemptive lamivudine can be safely withdrawn in order to achieve a more prolonged clinical benefit.[35] HBeAg negative patients with high serum HBV DNA may also require prolonged therapy with lamivudine as it has been shown that a sustained response can be achieved in HBeAg negative immunocompetent patients after a 2-year course of lamivudine therapy.[36]

However, this prolonged course of lamivudine in HBeAg positive and negative patients will increase the risk of developing lamivudine resistant mutants. The fact that lamivudine resistant mutants can be associated with rapid clinical deterioration after transplantation has raised additional concerns about prolonged lamivudine therapy in immunocompromised patients.[37][38] One way to overcome this problem is by using alternative nucleoside analogues that have a better resistance profile such as adefovir dipivoxil or entecavir. Recently, it has been shown that entecavir has stronger antiviral activity when compared with lamivudine and can result in a more profound suppression of viral replication. It also has a better resistance profile with no evidence of genotypic resistance in nucleoside analogues naïve patients after 48 weeks of therapy.[39] Therefore, further clinical trials with these agents or combination regimens with at least additive or preferably synergistic effects as preemptive therapy are warranted.[40]

One of the limitations of this study is the absence of a liver biopsy before commencement of lamivudine or chemotherapy. As Hong Kong is an endemic area for HBV infection, the most common mode of HBV infection is perinatal transmission.[41] Thus, many of the HBsAg positive patients in this study are likely to have been infected for four to five decades before developing hematological malignancy. As the baseline serum alanine aminotransaminase of the HBsAg positive patients are mostly within the normal range, it is unlikely that these patients had severe hepatic necroinflammation.[42] On the other hand, it is possible that some of these patients had a more advanced stage of fibrosis at presentation accounting for the esophageal varices in 1 of the patients. This would be better characterized if one could have baseline liver biopsy for these patients. However, it would be difficult to justify such procedure in high-risk patients with no specific clinical indication, such as derangement of liver function test.

Finally, based on our experience and the currently available data, we would recommend that all patients undergoing intense cytotoxic chemotherapy be screened for HBsAg. HBsAg positive patients, especially those at a higher risk of developing HBV reactivation; patients receiving steroid containing chemotherapy, hematopoietic stem cell transplantation, high prechemotherapy serum HBV DNA, high intrahepatic cccDNA and HBeAg positivity; be started on preemptive lamivudine 1 week before initiation of chemotherapy.[43][44][45][46] They should be closely monitored at every 4 weeks while on chemotherapy for breakthrough hepatitis and HBV viral resistance. Preemptive lamivudine should cover the entire duration of chemotherapy and can be safely withdrawn in HBeAg negative patients with low prechemotherapy serum HBV DNA once recovery of white cell count has occurred. After withdrawal of preemptive lamivudine, we recommend close monitoring of their serum HBV DNA and
aminotransaminase levels for evidence of withdrawal flare every 4 weekly for the first 12 months. Lamivudine should be resumed once a 1-log_{10} increase in serum HBV DNA is detected. On the other hand, lamivudine should be continued until HBeAg seroconversion is achieved in HBeAg positive patients. Lamivudine should also be continued for a more prolonged duration in HBeAg negative patients with a prechemotherapy serum HBV DNA of more than 10^{4} copies/ml (Figure 4).

In conclusion, a high prechemotherapy serum HBV DNA is associated with an increased risk of HBV reactivation after withdrawal of preemptive lamivudine. The optimal duration of antiviral therapy may have to be prolonged in this subgroup of patients even after the completion of chemotherapy. Patients receiving preemptive chemotherapy should be closely monitored for a prolonged period of time as HBV reactivation leading to hepatic failure may still occur 3 months after the withdrawal of preemptive lamivudine.
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Figure Legend

Figure 1. Cumulative probability of HBV reactivation after withdrawal of preemptive lamivudine therapy.
Figure 2. Cumulative probability of HBV reactivation after withdrawal of lamivudine in (2A) HBV DNA status and (2B) HBeAg status.
Figure 3. Graphs showing serum HBV DNA and alanine aminotransaminase in 3 patients with hepatic failure due to HBV reactivation after withdrawal of lamivudine.
Figure 2A
HBV Reactivation After Withdrawal of Lamivudine

Figure 2B

- HBeAg Positive
- HBeAg Negative
Figure 3A
Figure 3B

Graph showing changes in HBV DNA (Log10 copies/ml) and Serum ALT (U/L) over time (in months). The graph includes a timeline from 0 to 18 months, with markers for LAMIVUDINE and CHEMOTHERAPY.

- **HBV DNA (Log10 copies/ml)**: Decreases initially and then remains relatively stable before increasing sharply by month 17.
- **Serum ALT (U/L)**: Shows a decrease initially, followed by an increase that peaks significantly by month 17.

While the text is not directly transcribed, the figure correlates the time points with specific changes in HBV DNA and Serum ALT levels, highlighting the impact of LAMIVUDINE and CHEMOTHERAPY treatments.
Figure 3C
Patients undergoing chemotherapy

Screening

HBsAg positive patients

"Pre-emptive" lamivudine therapy

Close monitoring every 4 weekly

Close surveillance for HBV viral resistance

Risk factors
- Chemotherapy-intense, steroid-containing
- Intense immunosuppression-transplantation
- High pre-chemo HBV DNA
- High intrahepatic cccDNA

HBeAg negative patients with HBV DNA < 10^4 copies/ml prechemotherapy

Withdrawal of lamivudine ≥ 3 months after the completion of chemotherapy when WBC has returned to prechemotherapy level

Monitor closely for withdrawal flare

HBeAg positive or HBeAg negative with HBV DNA ≥ 10^4 copies/ml

Continue lamivudine therapy until HBeAg seroconversion in HBeAg positive patients

Prolonged course of lamivudine in HBeAg negative patients with prechemotherapy HBV

Figure 4
Hepatitis B reactivation after withdrawal of pre-emptive lamivudine in patients with haematological malignancy upon completion of cytotoxic chemotherapy

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