Nucleos(t)ide analogues for preventing HBV reactivation in immunosuppressed patients with hematological malignancies: a network meta-analysis

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1 Introduction

Recurrence of hepatitis B virus (HBV) infection, induced by cytotoxic chemotherapy is a serious complication in cancer patients with chronic HBV (CHB) infection. Patients may suffer from varying degrees of liver injury and even hepatic failure, delaying chemotherapy and ultimately affecting patients’ survival, or death. Several conditions such as lymphoma, steroid-containing or anthracycline-containing systemic cytotoxic chemotherapy and biological agents (rituximab) were reported to be associated with HBV reactivation in cancer patients [1,2]. Hematopoietic stem cell transplantation (HSCT) has become the standard of care for various hematological malignancies. Due to a long-term immunocompromised state, HBV surface antigen (HBsAg)-positive patients receiving HSCT are exposed to a high risk for HBV reactivation in the absence of prophylactic anti-HBV treatment. Patients with hematological malignancies are more susceptible to HBV reactivation when treated with chemotherapy or in the context of HSCT.

Previous studies reported that the incidence of chemotherapy-induced HBV reactivation in HBsAg-positive patients with hematological malignancies ranged from 32.08% to 60%[3–6]. With this high incidence, recurrence of HBV infection in this specific population has drawn global attention. Antiviral prophylaxis during chemotherapy has been investigated extensively in the last two decades. Application of the oral nucleos(t)ide analog (NA), lamivudine for the treatment of CHB infection has demonstrated to inhibit HBV replication, decrease viral load in the serum, and improve hepatitis both clinically and histologically. A large number of studies also demonstrated a preventive effect of using lamivudine in CHB patients with hematological diseases during chemotherapy [3,5–8]. Because of the emergence of HBV mutants resistant to lamivudine, the prophylactic efficiency of lamivudine is deteriorating. Currently, the second and third generation of NAs, such as adefovir, telbivudine, entecavir, and tenofovir, has been available for clinical use. Some clinical trials were able to demonstrate the efficacy of these NAs for the prevention of HBV reactivation in CHB patients with lymphoma or leukemia when given chemotherapy [7,9,10].

According to the EASL 2012 guidelines for the management of HBV infection [11], preemptive therapy with lamivudine is recommended for HBsAg-positive patients with low (<2000 IU/ml) HBV DNA levels, when a finite and short...
duration of immunosuppression is scheduled. For patients with a high HBV DNA level, scheduled for a lengthy and repeated cycles of immunosuppression, prophylactic treatment with entecavir or tenofovir is recommended. The grading of recommendation in the EASL 2012 guidelines is strong, but the grading of evidence is low to very low because of the lack of evidence from head-to-head clinical trials which systematically compare the prophylactic effects of these five antiviral agents. Most trials conducted pairwise comparisons and only compared the prophylactic effect of one agent against lamivudine. Therefore, no powerful evidence is available to indicating the most effective regime for prevention of HBV reactivation in HBsAg-positive patients receiving chemotherapy. Theoretically, large-scale head-to-head randomized controlled trials (RCTs) with multiple comparator arms should be conducted to solve this problem. Network meta-analysis may be a potential method to advance our understanding of the most efficacious intervention. Network meta-analysis enables the combination of the direct and indirect evidence by using a common comparator, ultimately facilitating jointly comparing of multiple treatments.

With regard to the limitations of the published trials, the aim of our study is to conduct a systematic review and network meta-analysis to simultaneously evaluate the efficacy of five oral NAs (entecavir, adefovir, telbivudine, tenofovir, and lamivudine), for the prevention of HBV reactivation and HBV-related complications in CHB patients with hematological malignancies undergoing chemotherapy.

2 Methods

2.1. Search strategy

A computerized literature search was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. Literature searches were conducted using PubMed, Embase, and the Cochrane Library (prior to Aug 31, 2015) using the following keywords and subject terms: [hepatitis B’ (MeSH) or HBV or Hep B virus or Hep B] and [reactivation] and [lamivudine’ (MeSH) or ‘entecavir’ (MeSH) or ‘adefovir’ (MeSH) or ‘telbivudine’ (MeSH) or ‘tenofovir’ (MeSH)]. The search strategy of PubMed database was described in greater detail in Supplementary Appendix A. Meeting abstracts, references of retrieved articles, relevant meta-analyses and systematic reviews were also explored. Case reports, editorials, letters, and review articles were not reviewed. The search was limited to English articles. Independent assessment of abstracts was performed for each article by 2 reviewers (Min-Yue Zhang and Gui-Qi Zhu).

2.2. Selection criteria

The following selection criteria should be met: (1) study design was RCT, retrospective or prospective cohort control study; (2) HBsAg-seropositive patients with hematological malignancies undergoing chemotherapy or HSCT; (3) trials comparing the effect of prophylactic treatment with five oral NAs (lamivudine, entecavir, adefovir, telbivudine, and tenofovir) or no prophylactic anti-HBV treatment, prevention of HBV reactivation and HBV-related complications during chemotherapy or HSCT. Not eligible for inclusion were: (1) studies of noncancer patients receiving immunosuppression therapy, including organ transplantation, inflammatory bowel disease, asthma, and autoimmune diseases patients; (2) studies of patients with nonhematological malignancies; (3) studies of patients with coinfection of human immunodeficiency virus (HIV) or other hepatitis viruses (HCV, hepatitis D virus [HDV]); (4) studies of patients with an occult HBV infection [HBsAg negative and hepatitis core antibody (HbcAb) positive]; (5) patients who received oral NAs treatment before. In the case several publications overlapped, only the study with the most detailed and/or most recent content was included.

The primary outcome of this study was incidence of HBV reactivation, which was defined by an increase in HBV DNA level to 10-fold or more compared with baseline level, or the appearance of HBV-DNA in previously negative patients or an absolute increase of HBV DNA exceeding 10^5 ge/mL in the absence of other systemic infection [12]. The secondary outcome measures included: (1) HBV-related hepatitis, defined as a more than 3-fold increase in ALT that exceeded the upper normal limit (UNL) or an absolute increase of ALT to over 100 IU/L and having the evidence of HBV reactivation without other apparent causes of hepatitis; (2) hepatitis, defined as more than 3-fold increase in ALT that exceeded the UNL or an absolute increase of ALT to over 100 IU/L; (3) HBV-related death, defined as death of a patient who had documented HBV reactivation without other apparent cause of death; (4) all causes of death.

2.3. Data extraction

An electronic data record form was used to independently extract the data and outcomes by two reviewers (Min-Yue Zhang, Gui-Qi Zhu). In case discrepancies on data extraction arose, an additional arbiter, Ming-Hua Zheng was consulted. The following information was recorded: (1) author’s name, (2) year of publication, (3) country, (4) study design, (5) types of hematological malignancy, (5) prophylactic interventions, (6) patients’ characteristics, including age, total numbers of patients, the numbers of male patients, duration of prophylaxis and follow up. If some relevant information and outcomes were unavailable directly from the study, the relevant corresponding authors were contacted by email or telephone for assistance.

2.4. Quality assessment

Methodological quality was evaluated independently by 2 reviewers (Min-Yue Zhang, Gui-Qi Zhu) adopting the Newcastle-Ottawa Quality Assessment Scale. Three major components of each study, including patient selection, comparability of interventions and observations group, and assessment of outcome, were examined to assess the quality of the included studies (Supplementary Table 1).
2.5. Data analysis

First, the pairwise meta-analysis using Stata software (version 10.0, StataCorp, College Station, TX) was conducted. Then a network meta-analysis was performed to compare five prophylaxis regimes (lamivudine, entecavir, adefovir, telbivudine, and tenofovir) in addition to no prophylaxis using Markov chain Monte Carlo methods in WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom). The methods of pairwise meta-analysis and network meta-analysis were detailed in our previous publication [33].

3 Results

3.1. Study characteristics

Of the 3555 potentially relevant publications reviewed by our literature search, 488 manuscripts were identified through title and abstract screening. After further assessment of the full text or abstracts, we included 28 manuscripts (29 trials) [3–10,13–32] with a total of 1478 patients for meta-analysis. Figure 1 summarized the detailed procedure of the search and selection. Of the included trials, 3 were RCTs, 22 were retrospective cohort trials, and 4 were prospective cohort trials. The patients in most trials suffered from lymphoma. The patients in six studies received allogeneic HSCT (allo-HSCT). In terms of study arms, there were three trials [7,10,32] with more than 2 comparator arms, and the rest consisted of 2 study arms. In total, 954 HBsAg sero-positive patients received one of the five oral NAs as prophylaxis during chemotherapy or allo-HSCT. 524 HBsAg-positive patients did not receive any prophylactic treatment. A summary of characteristics of the included studies was presented in Table 1. Supplementary Table 2 showed the results of the quality assessment of eligible studies, suggesting that the quality of included studies was reliable. The network of all treatment comparisons analyzed for the primary and secondary outcomes was demonstrated in Figure 2. The funnel plots for the different prophylactic regimens network, in terms of clinical outcomes, were presented in Supplementary Figure 1, suggesting that there was no evidence of publication bias. No significant heterogeneity was found in the traditional meta-analysis except for the comparison of HBV reactivation between entecavir and no prophylaxis (see Table 2).

3.2. HBV reactivation

In total, 46 comparisons, including all 6 interventions contributed to the analysis of the incidence of HBV reactivation. A total of 596 patients (56.49%) were assigned to lamivudine prophylaxis, 163 (15.45%) to entecavir prophylaxis, 4 (0.38%) to telbivudine prophylaxis, 11 (1.04%) to adefovir prophylaxis, 26 (2.46%) to tenofovir prophylaxis and 255 (24.18%) of the patients did not receive any prophylactic intervention.

The results of the network meta-analysis for this outcome were illustrated in Figure 3(a). With the exception of
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Country [Reference]</th>
<th>Types of hematological malignancy</th>
<th>Intervention A vs. B</th>
<th>Treatment duration (m)</th>
<th>Median (range) or Mean ± SD</th>
<th>Age (y)</th>
<th>Median (range) or Mean ± SD</th>
<th>Total No (n)</th>
<th>Male No (n)</th>
<th>Follow up (m)</th>
<th>Median (range) or Mean ± SD</th>
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<tbody>
<tr>
<td>Lau et al., 2003 [4]</td>
<td>China Hong Kong</td>
<td>Lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: 7 days prior to chemo End: 6 weeks after the completion of chemo</td>
<td>50.6 (23 – 98) vs. 51.2 (24 – 98)</td>
<td>15 vs. 15</td>
<td>8 vs. 9</td>
<td>&gt;3</td>
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<tr>
<td>Hsu et al., 2008 [5]</td>
<td>China Taiwan</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: day 1 of chemo End: 2 months after the completion of chemo</td>
<td>50.5 (32–67) vs. 41 (20–74)</td>
<td>26 vs. 25</td>
<td>12 vs. 13</td>
<td>33.2 vs. 38.6 (median)</td>
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<td>Huang et al., 2014 [9]</td>
<td>China</td>
<td>Diffuse large B cell lymphoma</td>
<td>LAM 100 mg/d vs. ETV 0.5 mg/d</td>
<td>Start: 7 days prior to chemo End: 6 months after the completion of chemo</td>
<td>46 (25–76) vs. 41 (19–66)</td>
<td>60 vs. 61</td>
<td>37 vs. 31</td>
<td>40.7 (8.6–62.3)</td>
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<td>Persico et al., 2002 [13]</td>
<td>Italy</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: during chemo End: 2 months after the completion of chemo</td>
<td>Total 45 (38–61)</td>
<td>3 vs. 18</td>
<td>Total 11</td>
<td>18</td>
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<td>Korea</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>N/A</td>
<td>44 (29–68) vs. 47.5 (18–70)</td>
<td>11 vs. 20</td>
<td>6 vs. 13</td>
<td>NA</td>
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<td>Leaw et al., 2004 [3]</td>
<td>China Taiwan</td>
<td>Aggressive lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: initiation of chemo End: 1 month after the completion of chemo</td>
<td>N/A</td>
<td>11 vs. 53</td>
<td>N/A</td>
<td>24 (2–120)</td>
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<td>Orszulick et al., 2004 [15]</td>
<td>Turkey</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: before chemo</td>
<td>44 (35–49) vs. 42.5 (14–72)</td>
<td>4 vs. 8</td>
<td>3 vs. 3</td>
<td>N/A</td>
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<td>Lim et al., 2007 [8]</td>
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<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>End: 3–6 months after the completion of chemo</td>
<td>N/A</td>
<td>24 vs. 21</td>
<td>N/A</td>
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<tr>
<td>Chen et al., 2008 [16]</td>
<td>China</td>
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<td>LAM 100 mg/d vs. CON</td>
<td>N/A</td>
<td>13 vs. 11</td>
<td>N/A</td>
<td>28.2 (mean)</td>
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<td>Japan</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>N/A</td>
<td>10 vs. 15</td>
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<td>Yeo et al., 2009 [18]</td>
<td>China Hong Kong</td>
<td>Diffuse large B cell lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>N/A</td>
<td>15 vs. 9</td>
<td>N/A</td>
<td>N/A</td>
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<td>Koo et al., 2010 [19]</td>
<td>Singapore</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>N/A</td>
<td>18 vs. 8</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Topcuoglu et al., 2010 [20]</td>
<td>Turkey</td>
<td>Allo-HSCT patients</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: initiated with conditioning regimen End: 6–12 month after the cessation of immunosuppression at posttransplant period</td>
<td>Total median 33</td>
<td>14 vs. 9</td>
<td>Total 22</td>
<td>N/A</td>
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<td>Pei et al., 2010 [21]</td>
<td>China Taiwan</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: prior to chemo End: 0–9 month (range) months after cessation of rituximab treatment (median 2 month)</td>
<td>49 (31–72) vs. 54 (40–81)</td>
<td>5 vs. 10</td>
<td>2 vs. 5</td>
<td>N/A</td>
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<td>Mya et al., 2012 [22]</td>
<td>Singapore</td>
<td>Multiple myeloma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: before chemo End: 6–12 months after the completion of chemo</td>
<td>N/A</td>
<td>11 vs. 4</td>
<td>N/A</td>
<td>Median 33.6</td>
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<td>Chen et al., 2012 [6]</td>
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<td>Diffuse large B cell lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: 7 days prior to chemo End: 3 months after the completion of chemo</td>
<td>47 (21–76) vs. 46.9 (22–76)</td>
<td>30 vs. 20</td>
<td>19 vs. 11</td>
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(Continued)
Table 1. (Continued).

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<th>Study, Year [Reference]</th>
<th>Country</th>
<th>Types of hematological malignancy</th>
<th>Intervention A vs. B</th>
<th>Treatment duration (m) Median (range) or Mean ± SD</th>
<th>Intervention A vs. B</th>
<th>Age (y) Median (range) or Mean ± SD</th>
<th>Total No (n)</th>
<th>Male No (n)</th>
<th>Follow up (m) Median (range) or Mean ± SD</th>
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<td>Li et al., 2011 [23]</td>
<td>China</td>
<td>Lymphoma</td>
<td>LAM 100 mg/d vs. ETV 0.5 mg/d</td>
<td>Start: 7 days prior to chemo 46 (20–81) VS. 44 (17–74)</td>
<td>89 vs. 34</td>
<td>52 vs. 22</td>
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<td>Chen et al., 2013 [24]</td>
<td>Australia</td>
<td>Hematological malignancies</td>
<td>LAM 100 mg/d vs. ETV 0.5 mg/d</td>
<td>N/A</td>
<td>N/A</td>
<td>11 vs. 4</td>
<td>N/A</td>
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<td><strong>Retrospective cohort study with historical control group</strong></td>
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<td>Lau et al., 2002 [25]</td>
<td>China Hong Kong</td>
<td>Allo-HSCT patients</td>
<td>LAM 100 mg/d vs. CON</td>
<td>38.5 (13–54) vs. 32 (5–48)</td>
<td>20 vs. 20</td>
<td>10 vs. 16</td>
<td>&gt;12</td>
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<td>Li et al., 2006 [26]</td>
<td>China</td>
<td>Lymphoma</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: 7 days prior to chemo End: 8 weeks after the completion of chemo 40 (16–74) VS. 41 (12–75)</td>
<td>40 vs. 116</td>
<td>26 vs. 72</td>
<td>&gt;3</td>
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<td>Hsiao et al., 2006 [27]</td>
<td>China Taiwan</td>
<td>Allo-HSCT patients</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: 0–62 weeks (range) prior to allo-HSCT, 11 weeks (median) End: posttransplantation period 41 (19–56) (LAM)</td>
<td>16 vs. 55</td>
<td>12 (LAM)</td>
<td>39 (2–216)</td>
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<td>Huang et al., 2009 [28]</td>
<td>China</td>
<td>Allo-HSCT patients</td>
<td>LAM 100 mg/d vs. CON</td>
<td>Start: 7 days prior to chemo End: 6 months after the completion of allo-HSCT 37 ± 12 ± 29 ± 9</td>
<td>20 vs. 12</td>
<td>13 vs. 7</td>
<td>12.3 vs. 43.8 (median)</td>
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<td><strong>Prospective cohort studies</strong></td>
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<td>Shibolet et al., 2002 [29]</td>
<td>Israel</td>
<td>Lymphoma</td>
<td>LAM 150 mg/d vs. CON</td>
<td>Start: prior to initiation of chemo End: 6 months after the completion of chemo 55 (38–65) VS. 57.5 (46–67)</td>
<td>7 vs. 4</td>
<td>4 vs. 4</td>
<td>N/A</td>
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<td>Kim et al., 2013 [7]</td>
<td>Asian</td>
<td>B cell lymphoma</td>
<td>LAM vs. ETV</td>
<td>N/A</td>
<td>N/A</td>
<td>28 vs. 16</td>
<td>/</td>
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<td>Gentile et al., 2014 [30]</td>
<td>Italy</td>
<td>Hematological malignancies</td>
<td>LAM vs. TDF</td>
<td>32 (9–72) vs. 24 (4–48)</td>
<td>N/A</td>
<td>13 vs. 25</td>
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<td><strong>Prospective cohort studies with historical control group</strong></td>
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<td>Hui et al., 2005 [31]</td>
<td>China Hong Kong</td>
<td>Allo-HSCT patients</td>
<td>LAM vs. CON</td>
<td>Start: 7 days prior to allo-HSCT End: 52 weeks after allo-HSCT or until death 42 (23–38) (LAM)</td>
<td>19 vs. 14</td>
<td>10 (LAM)</td>
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<td><strong>Multi-arms trials</strong></td>
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<td><strong>Retrospective cohort study</strong></td>
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<tr>
<td>Kim et al., 2013 [7]</td>
<td>Asian</td>
<td>B cell lymphoma</td>
<td>ADV vs. ETV vs. LAM vs. CON</td>
<td>N/A</td>
<td>N/A</td>
<td>7 vs. 31 vs. 96 vs. 22</td>
<td>N/A</td>
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<tr>
<td>Chen et al., 2015 [10]</td>
<td>China Taiwan</td>
<td>Acute myeloid leukemia</td>
<td>LAM vs. ETV vs. ADV vs. LdT vs. TDF vs. CON</td>
<td>Start: At diagnosis of leukemia End: 12 months after the completion of chemo 23 vs. 11 vs. 2 vs. 2 vs. 1 vs. 11</td>
<td>N/A</td>
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<td>Lu et al., 2015 [32]</td>
<td>China</td>
<td>Diffuse large B cell lymphoma</td>
<td>LAM vs. ETV vs. ADV vs. LdT vs. CON</td>
<td>N/A</td>
<td>N/A</td>
<td>96 vs. 6 vs. 2 vs. 2 vs. 24</td>
<td>N/A</td>
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</table>

CON: control (no prophylaxis); LAM: lamivudine; ETV: entecavir; ADV: adefovir; LdT: telbivudine; TDF: tenofovir; Allo-HSCT: allogeneic hematopoietic stem cell transplantation.
telbivudine, all active interventions showed a significant efficacy in reducing the incidence of HBV reactivation when compared with no prophylactic therapy. In the comparisons between different anti-HBV regimes, both entecavir and tenofovir were remarkably better than lamivudine, telbivudine, and adefovir. Although the difference was not significant, there was a trend that tenofovir was superior to entecavir [odds ratio (OR) 0.16, 95% confidence intervals (CIs) 0.00 ~ 2.62].

Figure 4(a–f) shows the distribution of the probabilities of each prophylactic interventions ranked for each of the possible six positions. Tenofovir had the best probability (90%) for the optimal prophylactic regime in reducing the incidence of HBV reactivation followed by entecavir (88%).

### 3.3. HBV-related hepatitis

Eighteen comparisons, including 3 interventions assessed the efficacy of the prevention of HBV-related hepatitis. Overall, 386 patients (48.92%) were assigned to lamivudine prophylaxis, 99 (12.55%) to entecavir prophylaxis and 304 (38.53%) patients did not receive any prophylactic intervention.

### 3.4. HBV-related death

A total of 21 comparisons, including 4 interventions were available to analyze this outcome. Overall, 411 patients (51.44%) were assigned to lamivudine prophylaxis, 85 (10.64%) to entecavir prophylaxis, 7 (0.88%) to adefovir prophylaxis and 296 (37.04%) patients did not receive any prophylactic treatment.

The ORs with 95% CIs for this outcome by network meta-analysis were shown in Figure 3(c). Lamivudine (OR 0.33, 95% CI 0.16 ~ 0.72) as well as entecavir prophylaxis (OR 0.12, 95% CI 0.01 ~ 0.71) were significantly better than control. Although no significant difference existed, adefovir tended to be more favorable to reduce the incidence of HBV-related death than lamivudine (OR 0.37, 95% CI 0.03 ~ 2.06) or entecavir (OR 0.52, 95% CI 0.02 ~ 30.09). Figure 4(a–d) showed the distribution of probabilities of each prophylactic intervention, ranked at each of the possible four positions. Entecavir demonstrated to be the most effective intervention among these prophylactic treatments with the best probability (61%) in terms of outcome.
3.5. All causes of hepatitis

Fourteen comparisons, including 3 interventions provided data for the outcome of all causes of hepatitis. Totally, 355 patients (46.53%) were assigned to lamivudine prophylaxis, 99 (12.98%) to entecavir prophylaxis and 409 (40.49%) patients did not receive any prophylactic regimes.

The pool estimates for the outcome of the network meta-analysis were illustrated in Figure 3(d). Compared with no prophylaxis, both lamivudine (OR 0.19, 95% CI 0.10 ~ 0.34) and entecavir (OR 0.05, 95% CI 0.01 ~ 0.19) prophylactic treatment was significantly superior to this outcome. Furthermore, entecavir (OR 0.26, 95% CI 0.08 ~ 0.90) was able to be significantly superior than lamivudine in decreasing the incidence of hepatitis. Figure 4(a–c) shows the distribution of probabilities of each prophylactic interventions, ranked at each of the possible three positions. Entecavir had the best highest probability (98%) in decreasing the rates of all causes of hepatitis.

3.6. All causes of death

In total, 11 comparisons, including 3 interventions were available to analyze this outcome. 267 patients (44.87%) were assigned to lamivudine prophylaxis, 34 (5.71%) to entecavir prophylaxis and 294 (49.42%) patients did not receive any prophylactic intervention.

Figure 3(b) illustrated the ORs with 95% CI of the outcome of the network meta-analysis. Both lamivudine (OR 0.10, 95% CI 0.05 ~ 0.20) and entecavir prophylaxis (OR 0.01, 95% CI 0.00 ~ 0.06) demonstrated significant superiority over no prophylaxis. Entecavir (OR 0.10, 95% CI 0.01 ~ 0.52) could significantly prevent HBV-related hepatitis when compared with lamivudine. Figure 4(a–c) shows the distribution of probabilities of each prophylactic intervention, ranked at each of the possible three positions. Entecavir had the best probability (100%) in terms of reducing the incidence of HBV-related hepatitis.

Figure 3(e) showed the results of the indirect comparison of the outcome of reducing the incidence of all causes of death. Patients receiving lamivudine prophylaxis demonstrated to dramatically reduce the rate of death compared with no prophylaxis (OR 0.26, 95% CI 0.10 ~ 0.59). There was a trend that entecavir also appeared to be more effective than control (OR 0.28, 95% CI 0.01 ~ 0.70) and had the similar prophylactic effect as lamivudine (OR 1.08, 95% CI 0.02 ~ 25.42). Figure 4 (a–c) showed the distribution of probabilities of each...
prophylactic interventions being ranked at each of the possible three positions. Lamivudine was ranked as the best regime for reducing the incidence of overall death.

3.7. Comparisons between traditional pairwise and Bayesian network meta-analyses

The results of traditional pairwise and network meta-analyses were summarized in Table 2. The CIs and pooled estimates for the outcome from traditional pairwise meta-analyses and from network meta-analyses were consistent for most comparisons except for a few comparisons for the outcome of HBV reactivation due to small sample size. Table 3 showed the assessment of inconsistency by node splitting between direct and indirect evidence for outcomes of HBV reactivation and HBV-related death. There was no significant inconsistency within the networks for most treatment comparisons. As for the outcomes of all causes of death, all causes of hepatitis and HBV-related hepatitis, no closed loops which directly compared 3 treatments were found. Therefore, an inconsistency assessment could not be performed by node splitting method. The results of direct and indirect comparisons were in general consistently compatible for these three outcomes.

4 Discussion

Immunosuppressive therapy-induced HBV reactivation is a well-described complication in cancer patients with HBV infection. The risk of HBV reactivation differs according to the clinical settings. Compared with a healthy population and other tumor patients, lymphoma patients had a higher prevalence of a HBV carrier state [34]. With regard to lymphoma treatment, glucocorticoid and anthracycline-containing systemic cytotoxic chemotherapies are also known to increase the risk of HBV reactivation. Therefore, lymphoma is considered to be one of the significant risk factors associating with HBV reactivation during chemotherapy [35]. In allo-HSCT, the receipt bone marrow is substituted by donor bone marrow after myeloablation with high doses of chemotherapy. The recipients need to be treated with immunosuppressants for a long term. HBV reactivation is universal among patients undergoing allo-HSCT due to the extreme immunosuppressive state. Based on the high risk of HBV reactivation in these two immunosuppressed populations, we performed a network meta-analysis to evaluate the prophylactic efficacy of five oral NAs on immunosuppressive therapy-induced HBV reactivation and potential hepatitis and death in CHB infected patients with hematological malignancies. The results suggested that tenofovir and entecavir appeared to be the most potent oral antiviral agents to prevent HBV reactivation.
Due to the high incidence and serious complications of immunosuppressive therapy-induced HBV reactivation, anti-HBV prophylaxis has gradually aroused the clinicians’ attention. Lamivudine has been widely used to prevent HBV reactivation during chemotherapy for many years. Previous two traditional meta-analyses assessed the overall benefits of preventive lamivudine therapy in lymphoma patients. Ziakas et al. [36] found that compared with no prophylaxis, lamivudine was associated with a significant reduction in HBV reactivation by 79% in HBsAg-positive patients and a trend in reduction of HBV-related death by 32%. Furthermore, prolonging lamivudine prophylaxis could improve survival rates by 2.4%. In another pairwise meta-analysis [37], additional to a reduction of the rate of HBV reactivation, the incidence of hepatitis and the incidence of hepatitis related to HBV reactivation, the overall mortality and mortality attributable to HBV reactivation were significantly decreased in patients receiving prophylactic lamivudine compared with the control group. With the appearance of HBV mutants resistant to lamivudine, other oral NAs have been gradually available to clinicians for the prevention of HBV reactivation. In one RCT [9], patients prophylactically treated with entecavir had a beneficial effect on reducing the rate of HBV-related hepatitis and HBV reactivation when compared with lamivudine in HBsAg seropositive patients with diffuse large B cell lymphoma during chemotherapy. The findings of these traditional meta-analysis or RCTs were consistent with our findings.

There are several strengths in this network meta-analysis. First, to our knowledge, this is the first study that provides a useful and comprehensive picture for propensity of all available anti-HBV regimens preventing immunosuppressive therapy-induced HBV reactivation among CHB patients with hematological malignancies. Compared with the pairwise meta-analysis, that was only suitable for a direct comparison of individual pairs of intervention, this network meta-analysis combining 1478 patients allowed both direct and indirect comparisons of all available strategies in a single analysis. Second, with regard to the power of different NAs to decrease the incidence of HBV reactivation and other HBV-related complications, a formal rank order for prophylaxis strategies was provided by network meta-analysis, providing scientific evidence to clinicians in the choice of prophylactic regimens. In addition, in order to reduce concerns regarding potential inconsistency, an inconsistency diagnostic analysis was conducted by node-splitting for hexagon and quadrilateral loops.

The strengths of this network meta-analysis should be weighed against following limitations. First, there were some risks for bias in the included studies in terms of study design. Due to the limited number of published RCTs, we mainly included the prospective and retrospective cohort studies in our study. The methodological quality of these cohort studies was moderate to high by quality assessment. Additionally, patients’ characteristics, such as patient populations, duration of prophylaxis and follow-up, time of HBV reactivation, chemotherapy regimens and definitions of outcomes might be a source of bias in the analysis. However, the results of heterogeneity test in our study suggested to be acceptable. Second, the conclusion that tenofovir was the most effective prophylactic anti-HBV drug to prevent HBV reactivation was based on two non-randomized studies, one comparing lamivudine vs. tenofovir (n = 25) and one comparing lamivudine vs. entecavir vs. adefovir vs. telbivudine vs. tenofovir (n = 1). 95%CI of ORs of tenofovir in preventing HBV reactivation varied. Caution is required related to the small sample size and the paucity of RCTs on the use of NAs other than lamivudine in the prevention of immunosuppressive therapy-induced HBV reactivation. In addition, with the exception of HBV reactivation, tenofovir was not included to evaluate in all other outcomes. Based on the current available evidence, we concluded that entecavir appeared to be the most potent NAs to prevent HBV related morbidity and mortality. In the future, the effect of tenofovir to prevent HBV related morbidity and mortality in this population should be evaluated. Third, since data about adverse effects of NAs could not be obtained from most included studies, the adverse effect of the different drugs could not be assessed in depth.

In summary, this network meta-analysis demonstrates the superiority of using anti-HBV prophylaxis in preventing HBV reactivation for CHB patients with hematological malignancies receiving immunosuppressive treatment. Among available NAs, tenofovir and entecavir might be the two optimum regimens for reducing the risk of HBV reactivation.

**Key issues**

- Related with chemotherapy-induced or HSCT-induced immunosuppression, HBV related patients have a high rate of HBV reactivation without prophylactic anti-HBV treatment.
- Several oral NAs have been proposed to avoid HBV reactivation in CHB infected patients with hematological malignancies receiving chemotherapy or HSCT.
- Due to the lack of evidence from head-to-head RCT with multiple comparator, the clinical effects of prophylactic NAs are unclear.
- No powerful evidence is currently available indicating the most effective regime for prevention of HBV reactivation in HBsAg-positive patients receiving chemotherapy.
- Tenofovir and entecavir might be the most potent regimes in prevention of HBV reactivation for CHB infected patients with hematological malignancies undergoing chemotherapy or HSCT.

**Funding**

This work was supported by grants from National Natural Science Foundation of China (81500665), Scientific Research Foundation of Wenzhou (Y20160223), High Level Creative Talents from Department of Public Health in Zhejiang Province, and Project of New Century 551 Talent Nurturing in Wenzhou.

**Notes on contributor**

Author contributions: Zhang MY, Zhu GQ, Shi KQ, Chen FY and Zheng MH designed the study. Zhang MY, Zhu GQ, Huang HH screened studies and
extracted data. Zhu QG and Zheng JN did the statistical analyses. Cheng Z prepared figures. Zhang MY, Zhu QG, Poucke SV, Huang HH, Chen FY and Zheng MH reviewed the results, interpreted data, and wrote the manuscript. All authors saw and approved the final version of the paper.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


- Demonstrates that compared with lamivudine, prophylaxis with entecavir resulted in a lower incidence of HBV-related hepatitis and HBV reactivation in CHB infection patients with diffuse large B-cell lymphoma undergoing R-CHOP chemotherapy.


- The guidelines recommends that for patients with a high HBV DNA level, scheduled for a lengthy and repeated cycles of immunosuppression, prophylactic treatment with entecavir or tenofovir is considered.


- Provides the definition of HBV reactivation: an increase in HBV DNA level to 10-fold or more compared with baseline level, the appearance of HBV-DNA in previously negative patients or an absolute increase of HBV DNA exceeding 109 ge/mL, in the absence of other systemic infection.


- Statistical theories and methods of pairwise meta-analysis and network meta-analysis were detailed in the publication.


- Assesses the clinical and virological factors for HBV reactivation: detectable baseline HBV DNA prior to the administration of cytotoxic chemotherapy, the use of steroids and a diagnosis of lymphoma or breast cancer.
