Clinics and Research in Hepatology and Gastroenterology (2015) 39, 80—92

Available online at ScienceDirect www.sciencedirect.com

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ORIGINAL ARTICLE

Prophylactic lamivudine to improve the outcome of HBsAg-positive lymphoma patients during chemotherapy: A systematic review and meta-analysis

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Available online 4 September 2014

Summary Hepatitis B viral (HBV) reactivation in lymphoma patients undergoing chemotherapy is associated with significant morbidity and mortality. Increasingly, lamivudine is being used to prevent hepatitis B reactivation. To assess the effects of prophylactic lamivudine on reactivation and mortality following chemotherapy in lymphoma patients who are hepatitis B surface antigen (HBsAg)-positive, we searched Medline/PubMed, Ovid MEDLINE, EMBASE, Web of Knowledge and the Cochrane Library for studies through November 2013. Statistical analysis was performed using REVMAN. Fourteen studies consisting of 636 patients were included in the analysis. The rate of HBV reactivation, incidence of hepatitis and incidence of hepatitis due to HBV reactivation in patients with lamivudine prophylaxis was significantly lower than those with no prophylaxis. Risk ratios [RRs] were 0.25 (95% confidence intervals [CI] 0.13—0.51; $P = 0.0001$), 0.40 (95% CI 0.26—0.63; $P < 0.0001$), and 0.21 (95% CI 0.09—0.51; $P = 0.0005$) respectively. In addition, patients given prophylactic lamivudine had significant reductions in overall mortality and mortality attributable to HBV reactivation compared with control group. Risk ratios [RRs] were 0.45 (95% CI 0.29—0.70; $P = 0.0004$) and 0.41 (95% CI 0.20—0.84; $P = 0.01$) respectively. Chemotherapy disruption was not significantly different between the two groups. Risk ratios

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http://dx.doi.org/10.1016/j.clinre.2014.07.010
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were 0.34 (95% CI 0.09—1.26; $P=0.11$). Prophylactic therapy with lamivudine for HBsAg-positive lymphoma patients who are undergoing chemotherapy may reduce the risk for HBV reactivation, hepatitis due to HBV reactivation, overall mortality and mortality attributable to HBV reactivation. Additionally, patients with preventive lamivudine had a trend towards the decreased incidence of chemotherapy disruption.
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Introduction

Hepatitis B infection, caused by the hepatitis B virus (HBV), is one of the most common infectious diseases worldwide and is a major global health problem, affecting more than 350 million persons worldwide [1,2]. Infection with HBV can lead to chronic liver disease, cirrhosis, and liver cancer [3]. The incidence of HBV reactivation in HBsAg-positive patients undergoing chemotherapy is 10—50% [4—10]. A growing number of published reports of HBV reactivation-related morbidity and mortality have made this population the focus of considerable investigation, including the role of prophylactic antiviral therapy [11—14].

Lamivudine, an oral nucleoside analogue, inhibits HBV replication and reduces viral load, leading to clinical, biochemical, serological and histological improvement in patients with chronic hepatitis B [15—17]. Lamivudine also has an excellent long-term safety profile and is generally well tolerated [18]. Despite receiving lamivudine as a therapeutic measure at the time of HBV reactivation, HBsAg-positive patients who develop HBV reactivation during chemotherapy may still suffer fatal hepatic injury [19—21]. Therefore, prophylaxis may be the key to effective management of HBV reactivation [19]. Administration of prophylactic or preemptive lamivudine or other nucleoside/nucleotide analogues before commencing chemotherapy seems to be a reasonable approach for preventing reactivation of HBV [20]. HBV reactivation has been described in chronic HBV carriers diagnosed with a variety of cancers who were treated with chemotherapy agents. However, the most commonly reported cases are patients with lymphoma [21—24]. In 2009, a meta-analysis including nine clinical studies evaluated the effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma patients. This preliminary meta-analysis showed that lamivudine prophylaxis is associated with a significant reduction in HBV reactivation and a trend in reducing HBV-related mortality [25]. However, the efficacy of prophylactic lamivudine in preventing hepatitis, hepatitis due to HBV reactivation, overall mortality and chemotherapy disruption is not reported. Furthermore, in recent years, several new trials comparing lamivudine prophylaxis with no prophylaxis for the outcome of HBsAg-positive lymphoma patients undergoing chemotherapy have been published [26—30].

Therefore, we conducted this meta-analysis to study the impact of lamivudine prophylaxis on HBsAg-positive lymphoma patients undergoing chemotherapy. Our hypothesis was that lamivudine prophylaxis reduces the rate of HBV reactivation, incidence of hepatitis and incidence of hepatitis attributable to HBV reactivation, overall and HBV reactivation-associated mortality and the rate of chemotherapy disruption.

Materials and methods

Literature search

We searched the following databases until November2013: Medline/PubMed, Ovid MEDLINE, EMBASE, Web of Knowledge and the Cochrane Library. Search terms were selected to maximize both the search sensitivity and specificity. The search strategy of the databases involved selecting subject headings and keywords used either alone or in combination: ''prophylaxis'', ''preemptive'', ''lamivudine'', ''hepatitis B virus'', ''HBV'', ''reactivation'', ''flare'', ''HBsAg'', ''chemotherapy'', ''lymphoma''. Any emerging discrepancies were resolved by consensus between two independent reviewers or with the help of a third author (Huai-dong Hu) via referencing the original article. The scope of the search was restricted to ''human'' and ''English''.

Inclusion and exclusion criteria

Inclusion criteria for the meta-analysis were:

- randomized controlled trials (RCTs), or retrospective or prospective cohort studies with a control (concurrent or historical) group;
- studies including a lamivudine prophylaxis group and a non-prophylaxis group;
- all lymphoma patients in the two groups had undergone chemotherapy and were seropositive for HBsAg.

Patient populations were excluded if:

- reactivation/flares were not related to HBV, or the HBV reactivation/flare was not a specific outcome of the study;
- did not involve chemotherapy;
- the study involved human immunodeficiency virus (HIV) co-infection;
- case reports or series and studies that included patients who had hepatitis D virus, hepatitis C virus or other liver diseases;
- did not have a lamivudine prophylaxis and non-prophylaxis group. Trials were also excluded if relevant data could not be extracted.

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