Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance

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CRD summary
The review found that lamivudine prophylaxis was associated with a significant decline in hepatitis B virus (HBV) reactivation and a trend in reduction of HBV-related deaths in lymphoma patients who received cancer chemotherapy. Limitations of the review methodology and reporting mean that the reliability of the conclusions is uncertain.

Authors' objectives
To evaluate the benefits of lamivudine prophylaxis on the risk of hepatitis B virus (HBV) reactivation and HBV-mortality in lymphoma patients receiving cancer chemotheraphy or immunotherapy who are hepatitis B surface antigen (HBsAg) carriers.

Searching
A search of MEDLINE (to December 2008) was performed. Search terms were listed in the review. A manual search of abstracts and bibliographies of review articles was performed.

Study selection
Randomised controlled trials (RCTs) or cohort studies that investigated the effect of lamivudine prophylaxis on HBV reactivation rate and HBV-related mortality after immunochemotherapy in patients with lymphoma were eligible for inclusion. Only studies from which relevant data could be extracted were eligible. Studies of non-lymphoma patients (including HIV co-infection) were not eligible for inclusion.

The studies in the review were prospective and retrospective; only one was randomised. Included studies used a lamivudine dose of 100mg/day except one that used (150mg/day). Where reported, treatment duration was between one and seven months and started at day one or at one week before the start of chemotherapy. The control intervention was not stated in the review.

Two reviewers independently selected the studies for inclusion; discrepancies were resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Relative risks (RR) and 95% confidence intervals (CI) for each study were calculated for re-activation and mortality.

Methods of synthesis
Pooled relative risks were calculated using Mantel Haenszel fixed-effect and DerSimonian and Laird random-effects models. Statistical heterogeneity between studies was measured using the $X^2$ Q test ($p<0.10$ denoted significant heterogeneity) and the $I^2$ statistic. Fixed-effect models were used in instances of limited heterogeneity and otherwise random-effects models were used.

Results of the review
Nine studies (396 participants) were included in the review.

Lamivudine prophylaxis was associated with a reduced risk of HBV reactivation (RR 0.21, 95% CI 0.13 to 0.35). There was no evidence of statistical heterogeneity between studies ($p=0.91$).

In eight studies (371 participants), lamivudine prophylaxis was not significantly associated with HBV-related mortality.
(RR 0.68, 95% CI 0.19 to 2.49). There was no evidence of statistical heterogeneity between studies (p=0.67).

Authors' conclusions
Lamivudine prophylaxis was associated with a significant decline in HBV reactivation and a trend in reduction of HBV-related deaths.

CRD commentary
The review question was clearly stated and inclusion criteria were adequately defined, but it was not clear from the review what treatment patients in the control arm of each study received. The authors did not appear to make an effort to identify unpublished data. The brief list of search terms meant that the search was unlikely to be comprehensive. The use of two reviewers for study selection reduced the risk of errors. There was no assessment of publication bias.

Insufficient details of individual trials (such as about the comparison arm and number and age of participants) were presented to enable a reader to assess the generalisability of the results. The number of studies included was relatively small; only 17 of the 396 participants in the review died, which could explain the lack of a statistically significant result for mortality. Although the authors planned to use a fixed-effect model in the absence of heterogeneity, it appeared that they used a random-effects model for the mortality analysis and a fixed-effect model for the re-activation analysis when neither showed statistical evidence of heterogeneity. As no validity assessment was performed, the reliability of the conclusions is uncertain.

Implications of the review for practice and research
Research: Future trials should analyse the results stratified by baseline characteristics of participants, such as HBV DNA, serum alanine aminotransferase (ALT) and hepatitis B e antigen status.

Practice: All HBsAg carriers should receive prophylactic antiviral treatment during immunochemotherapy, extended to include maintenance phase.

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