Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis

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CRD summary
The authors concluded that lamivudine prophylaxis reduces the rate of hepatitis B virus (HBV) reactivation and reactivation-related liver mortality in patients with chronic HBV undergoing chemotherapy for solid or haematological malignancies, though most of the primary studies were of questionable quality. The review was overall well-conducted and the results were consistent. These conclusions appear likely to be reliable.

Authors' objectives
To assess the effect of lamivudine prophylaxis for patients with hepatitis B virus (HBV) who are undergoing chemotherapy.

Searching
MEDLINE and the Cochrane Database of Systematic Reviews were searched from January 1995 to December 2006; the search terms were reported. The reference lists of retrieved studies and reviews were handsearched, as were abstracts from national hepatology and gastroenterology meetings. Studies reported in languages other than English were included, provided an abstract in English was available.

Study selection
The participants in eligible studies were chemotherapy patients with serological evidence of chronic or previous HBV. The ethnicity of the patients was not reported, but the majority of studies were conducted in Asia. Approximately half of the participants were female. The participants had a variety of solid tumours (including breast and nasopharyngeal) and haematological malignancies (including Hodgkin's and non-Hodgkin's lymphomas, leukaemia and multiple myeloma). Most received systemic chemotherapy using traditional drug regimens, many containing steroids. Patients in 2 studies underwent transarterial chemolipidolisation for hepatocellular cancer (HCC). All participants had either at least one positive serological marker of HBV (i.e. HBV surface antigen, HBV surface antibody or HBV core antibody) or had HBV-related HCC. At baseline, most of the participants had normal alanine aminotransferase (ALT) levels, 42% of patients in the intervention groups and 30% of controls were HBV deoxyribonucleic acid-positive, and about 20% of each group were positive for hepatitis B e antigen. Initially it was planned to also include studies of patients with HBV receiving a defined immunosuppressive therapy other than chemotherapy, but such studies were ultimately excluded because of heterogeneity and potential confounding factors. Studies of patients with human immunodeficiency virus coinfection were excluded. Eligible studies compared prophylaxis against HBV reactivation or flare with no prophylaxis. All studies utilised lamivudine 100 mg/day in the intervention group, starting (where stated) at the same time as chemotherapy, or at least a week beforehand, and continuing until the end of chemotherapy or (in most cases) for at least 4 weeks afterwards; in one case therapy continued for a year. Eligible studies were required to report HBV reactivation or flare as outcomes. The review also reported HBV reactivation-related liver mortality, all-cause mortality, and treatment delay or cessation due to HBV reactivation or any cause. Studies with a clearly described control or comparison group and defined follow-up were eligible for inclusion.

Two authors selected the studies, with any differences resolved by consensus.

Assessment of study quality
Study validity was assessed using the following criteria: description of withdrawals and drop-outs; clearly defined objectives, outcomes, inclusion and exclusion criteria, and interventions; use of a control group; and method to assess adverse events. One point was allocated for each criterion.

The authors did not state how the validity assessment was performed.
Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated from the numbers of events in the control and intervention groups of each study. Authors were contacted for more information if necessary.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were pooled using a random-effects model to calculate RRs and 95% CIs. Absolute risk reductions (ARRs) and the number of patients needing treatment in order to avoid one event (NNTs) were also calculated. Statistical heterogeneity was assessed using the $I^2$ statistic and the $\chi^2$ test (with $p<0.10$ denoting statistical significance for the latter). Clinical heterogeneity was discussed in the text.

Results of the review
Eleven studies (222 participants in the intervention groups and 399 in the control groups) were included in the review: 2 randomised controlled trials (n=102), 5 prospective cohorts (4 with historical controls) (n=425) and 4 retrospective cohorts (n=94).

Most of the studies scored 4 or 5 points for quality out of a possible 7. All studies had a control group and clearly defined objectives and interventions, ten had clearly defined outcome measures, six had clear inclusion and exclusion criteria, only two described withdrawals and drop-outs, and none described a method for assessing adverse events.

The intervention group was significantly less likely to experience HBV reactivation (10 studies) than the control group (RR 0.13, 95% CI: 0.07, 0.24, p<0.01; ARR -0.46, 95% CI: -0.61, -0.31, p<0.01). The NNT to prevent one reactivation was 3. There was no statistical heterogeneity associated with this finding ($I^2=0\%$). The results were similar, showing significant benefit for the intervention group, when the studies were stratified by the type of malignancy; there were 4 studies of patients with solid tumours (RR 0.13, 95% CI: 0.05, 0.34, p<0.01; ARR -0.32, 95% CI: -0.43, -0.22, p<0.01) and 4 studies of patients with haematological malignancies (RR 0.09, 95% CI: 0.03, 0.31, p<0.01; ARR -0.70, 95% CI: -0.92, -0.48, p<0.01).

Reactivation-related liver mortality (9 studies) was significantly less common in the intervention group than in the control group (RR 0.30, 95% CI: 0.1, 0.94, p=0.04; ARR -0.03, 95% CI: -0.07, 0.00, p=0.04). There was no statistically significant difference between the groups when the studies were stratified by the type of malignancy (solid or haematological), though there were no deaths in either intervention group (0 out of 63 and 0 out of 39) whereas there were deaths in the control groups (3 out of 67 and 2 out of 51).

There was no statistically significant difference between the groups for overall mortality (8 studies), either overall or when stratified by the type of malignancy.

Treatment delays were evaluated in 4 studies. When 3 studies were pooled, there were significantly less treatment delay or premature cessation of chemotherapy related to HBV reactivation in the intervention group than in the control group (RR 0.08, 95% CI: 0.02, 0.34, p<0.01; ARR -0.21, 95% CI: -0.43, 0.00, p=0.05). The pooling of 3 studies that reported treatment delays and premature cessation of chemotherapy for all causes also found a significant benefit for the intervention group (RR 0.41, 95% CI: 0.27, 0.63, p<0.01; ARR -0.24, 95% CI: -0.33, -0.15, p<0.01).

Authors' conclusions
The current rather limited evidence indicates that lamivudine prophylaxis reduces the rate of HBV reactivation and reactivation-related liver mortality in patients with chronic HBV undergoing chemotherapy for solid or haematological malignancies. Lamivudine also reduces the risk of interruption or premature termination of chemotherapy. Only three patients need to be treated to prevent one episode of reactivation.

CRD commentary
The study question and inclusion criteria were clear and appropriate sources were searched for studies, though the
electronic search was limited to two databases. Steps were taken to reduce the risk of error and bias in the study selection process by having two reviewers make decisions independently. However, it is unclear whether this also applied to the validity assessment and data extraction. Adequate details were provided about the individual studies, relevant criteria were used to assess study quality, and heterogeneity between the studies was appropriately evaluated. Potential sources of bias were well-addressed in the text. Despite some limitations in the reporting of study methods and the poor quality of most of the included studies, the review was overall well-conducted and the results were consistent. The authors’ conclusions appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians should appropriately screen for HBV before commencing chemotherapy (especially among patients at increased risk), and should initiate lamivudine prophylaxis in those who are HBV positive. It is unclear whether a safe viral threshold exists for starting chemotherapy, or what the optimum duration of prophylaxis is. Alternative prophylaxis may be needed in patients with a drug-resistant mutant virus.

Research: The authors stated that further research on the long-term use of antiviral therapy is needed.

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