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ORIGINAL ARTICLE

The efficacy of lamivudine prophylaxis against hepatitis B reactivation in breast cancer patients undergoing chemotherapy: A meta-analysis

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Background/Purpose: Lamivudine has been recommended as prophylaxis for the reactivation of hepatitis B virus (HBV) infection in patients undergoing chemotherapy. However, information on breast cancer patients in particular has been lacking. The purpose of this meta-analysis was to assess the overall efficacy of lamivudine prophylaxis compared to untreated patients with hepatitis B S-antigen (HBsAg) seropositive breast cancer who had undergone chemotherapy.
Methods: Studies that compared the efficacy of treatment with lamivudine prophylaxis *versus* no prophylaxis in HBsAg seropositive breast cancer patients were identified through Medline, Cochrane, and Embase databases.
Results: Six studies involving 499 patients were analyzed. The rates of HBV reactivation in patients with lamivudine prophylaxis were significantly lower than those with no prophylaxis (risk ratio [RR] = 0.23, 95% confidence interval [CI]: 0.13–0.39, $p < 0.00001$). Patients given lamivudine prophylaxis had significant reductions in the rates of hepatitis attributable to HBV

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compared with those not given treatment (RR = 0.20, 95% CI: 0.08—0.47, $p = 0.002$). The rates of moderate and severe hepatitis in patients with lamivudine prophylaxis were significantly lower compared with those patients who had not received prophylaxis (RR = 0.25, 95% CI: 0.10—0.62, $p < 0.003$; RR = 0.25, 95% CI: 0.10—0.59, $p = 0.002$). Patients given lamivudine prophylaxis had significantly fewer disruptions of chemotherapy (RR = 0.36, 95% CI: 0.21—0.64, $p = 0.0004$). There was no significant heterogeneity in the comparisons.
Conclusion: Lamivudine prophylaxis in HBsAg seropositive breast cancer patients undergoing chemotherapy is effective in reducing HBV reactivation and HBV-associated morbidity and mortality.

Introduction

Hepatitis B virus (HBV) infection is a major global public and medical concern. Seventy-five percent of infected individuals live in Southeast Asia and the western Pacific regions. Chronic carriers comprise more than 8% of the population in these regions.[1,2] The incidence of breast cancer (BC) is rising rapidly, especially in developing countries, in areas highly endemic with HBV, and therefore a high percentage of cancer patients (up to 12%) are chronic carriers of HBV.[3,4]

It is well recognized that patients who have a history of HBV infection are vulnerable to hepatitis flares during immunosuppressive or cytotoxic chemotherapy.[5—7] Exacerbation of hepatitis B can be a serious cause of morbidity and mortality in cancer patients undergoing chemotherapy. The clinical consequences vary from anicteric hepatitis to progressive hepatic failure.[8—11] Several mechanisms have been postulated for HBV flare-ups, such as chemotherapy-enhanced viral replication, corticosteroid-containing regimens, or return of immune competence after completion of chemotherapy.[12,13]

Over the few past decades, chemotherapy has played an important role in prolonging survival in BC patients. In patients receiving chemotherapy for BC, the incidence of HBV reactivation has been reported to be as high as 41—56%.[14—16] As an oral nucleoside reverse transcriptase inhibitor with activity against hepatitis B, lamivudine is effective in rapidly decreasing viral load, and is associated with few adverse effects.[17—21] Previous studies have demonstrated that lamivudine prophylaxis can effectively prevent HBV reactivation and its associated fatality during chemotherapy. A meta-analysis [22] by Lenna et al showed that patients given lamivudine prophylaxis had reductions of 87%, 70%, and 92% in HBV reactivation, reactivation-related mortality, and chemotherapy disruptions, respectively, compared with those patients not given prophylaxis. However, these studies were mainly based on patients with hematological malignancies. There have been few studies on BC patients. Several studies have reported on prophylaxis in hepatitis B S-antigen (HBsAg) seropositive BC patients who had undergone chemotherapy. In these studies, however, there were still several inconsistencies in the outcomes of hepatitis flares, HBV reactivation, reduction in the severity of hepatitis, and disruptions of chemotherapy between patients receiving lamivudine prophylaxis and those not treated.[15,23—26].

The purpose of this meta-analysis was to evaluate the efficacy of lamivudine prophylaxis on HBsAg seropositive BC patients undergoing chemotherapy.

Materials and methods

Literature search

Relevant studies were identified by searching Medline, Embase, and the Cochrane databases. The search strategy involved selecting subject headings and keywords used in combination or alone: lamivudine, cytotoxic chemotherapy, HBV, HBsAg, reactivation, flare, prophylaxis, breast cancer patients. The scope of the search was restricted to "human" and "English". We included all randomized controlled trials; cohort trials; and prospective, controlled, non-randomized trials. The search was carried out in March 2012, without a prior date limit for the search results. A detailed manual reference search of all relevant articles and reviews discovered in the database was used to identify potentially relevant articles missed by the computer search.

Inclusion and exclusion criteria

Inclusion criteria for the meta-analysis were as follows: (1) randomized controlled cohort, retrospective comparative case series and prospective, controlled, non-randomized studies; (2) studies including a lamivudine prophylaxis group and a non-prophylaxis group; and (3) all BC patients in the two groups had undergone chemotherapy and were seropositive for HBsAg. Patient populations were excluded if: (1) reactivation/flares were not related to HBV, or the HBV reactivation/flare was not a specific outcome of the study; (2) there was no immunosuppressive or cytotoxic therapy; (3) the study involved human immunodeficiency virus (HIV) co-infection; (4) the study included patients who had hepatitis D virus, hepatitis C virus or other liver diseases; (5) the study did not have a lamivudine prophylaxis or a treatment regimen; or (6) did not have a lamivudine prophylaxis and non-prophylaxis group. Any dataset for which insufficient analytic information was available was also excluded from the meta-analysis.

Efficacy measures

Hepatitis was defined as alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal or a >100 U/L increase over baseline based on a definition initially described by Lok et al and subsequently modified by Yeo et al.[4,27] Hepatitis attributable to HBV reactivation was defined as an increase