Hepatitis B surface antigen seroconversion after HBV reactivation in non-Hodgkin’s lymphoma

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Abstract

Reactivation of hepatitis B virus (HBV) can occur in lymphoma patients infected with HBV when they receive chemotherapy or immunotherapy. Prophylactic administration of lamivudine (LAM) reduces the morbidity and mortality associated with HBV reactivation. However, what defines HBV reactivation and the optimal duration of treatment with LAM have not yet been clearly established. HBV reactivation may occur due to the cessation of prophylactic LAM, although re-treatment with nucleoside analogs may sometimes result in hepatitis B surface antigen (HBsAg) seroconversion, which is a satisfactory endpoint for the management of HBV infection. We report a case of HBV reactivation in a 68-year-old HBsAg-positive patient who received rituximab-based immunomodulation for follicular lymphoma. HBV reactivation developed following cessation of prophylactic lamivudine therapy. The patient subsequently received treatment with entecavir (ETV), which led to a rapid and sustained suppression of HBV replication and HBsAg seroconversion. We also appraised the literature concerning HBV reactivation and the role of ETV in the management of HBV reactivation in lymphoma patients. A total of 28 cases of HBV reactivation have been reported as having been treated with ETV during or after immunosuppressive chemotherapy in lymphoma patients. We conclude that ETV is an efficacious and safe treatment for HBV reactivation following LAM cessation in lymphoma patients treated with rituximab-based immunomodulation.

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Key words: Hepatitis B surface antigen; Seroconversion; Non-Hodgkin’s lymphoma; Rituximab; Entecavir

Core tip: We describe the case of a 68-year-old hepatitis B surface antigen (HBsAg)-positive male patient who received rituximab-based immunochemotherapy for follicular lymphoma, and experienced hepatitis B virus (HBV) reactivation following cessation of lamivudine prophylaxis. Subsequent entecavir treatment produced rapid, sustained viral suppression and HBsAg seroconversion. Lamivudine prevents HBV reactivation but resistance rates may be as high as 17% in lymphoma patients. Available data suggest that entecavir is effective and safe for the treatment of HBV reactivation in lymphoma patients. Prophylactic antiviral therapy is recommended for patients with active or occult HBV infection following chemotherapy or immunomodulation. Potent antiviral drugs with a high genetic barrier to resistance should be considered in these cases.
in non-Hodgkin’s lymphoma. World J Gastroenterol 2014; 20(17): 5165-5170 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i17/5165.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i17.5165

INTRODUCTION

Hepatitis B virus (HBV) is highly prevalent in many malignancies, such as hepatocellular carcinoma and non-Hodgkin’s lymphoma (NHL)[1,2]. In recent years, rituximab, a chimeric monoclonal antibody directed against the CD20 antigen on B cells, has greatly improved the prognosis and outcome of patients with NHL[3,4]. However, rituximab induced profound and persistent depletion of the circulating population of B cells, leading to dysregulation of host immunity to HBV and increased risk of HBV reactivation[5,6]. Consequently, viral reactivation is an area of concern whenever an HBV-positive patient receives chemotherapy or immunotherapy[7]. Prophylactic administration of antiviral agents may reduce the incidence of HBV reactivation but flares do occur in 60% of patients following discontinuation of antiviral treatment[8]. We report a case of HBV reactivation following cessation of prophylactic lamivudine (LAM) in a patient with NHL who received rituximab-based treatment. Early administration of entecavir (ETV) successfully prevented further progression of HBV infection, leading to hepatitis B surface antigen (HBsAg) seroconversion.

CASE REPORT

A 68-year-old male was admitted to our hospital for follicular lymphoma in March 2009. He had chronic HBV infection for more than two decades. On admission, his alanine aminotransferase (ALT) levels were within the upper limit of normal (<40 U/L). The patient’s serology was found to be positive for HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B envelope antibody (anti-HBe), and hepatitis B core antibody (anti-HBc). However, he was HBeAg-negative. His HBsAg and anti-HBs titers were > 250 IU/mL and 45.81 mIU/mL, respectively, as measured by chemiluminescence microparticle immunoassays. His serum HBV DNA concentration was undetectable (limit of detection by polymerase chain reaction: 1000 copies/mL). The time course of the levels of liver enzymes and HBV DNA is shown in Figure 1.

From March 2009 to July 2009, administration of 5 cycles of immunotherapy (rituximab, fludarabine, cyclophosphamide) led to partial remission of the patient’s lymphoma. No additional treatment with anticancer drugs or corticosteroids followed. Prophylactic LAM (100 mg daily) was administered on the first day of immunotherapy and continued for 4 mo after completion of immunotherapy (total: 8 mo). In February 2010, 3 mo following cessation of LAM therapy, the patient’s HBV DNA level rose to $8.15 \times 10^3$ copies/mL. His ALT, HBsAg, and anti-HBs levels were 24 U/L, 121 IU/mL and 0.18 mIU/mL, respectively. Reactivation of HBV infection was considered and antiviral treatment with ETV 0.5 mg daily was administered immediately. In March 2010, 1 mo after ETV initiation and while still receiving ETV therapy, the patient’s HBV DNA concentration fell below detectable levels, while his ALT level increased to 62 U/L. In April 2010, 2 mo after ETV initiation, the patient achieved clearance of HBsAg and normalization of ALT levels. In July 2010, 4 mo after ETV initiation, the patient became anti-HBs-positive (titer: 13.5 mIU/mL), indicating HBsAg seroconversion. In December 2010, 7 mo after HBsAg seroconversion, ETV treatment was stopped (total: 10 mo). In March 2011 (4 mo after discontinuing ETV treatment), his HBsAg level was still negative and the patient’s anti-HBs titer had increased to 93.6 mIU/mL. The patient’s ALT levels remained normal and his HBV DNA level was undetectable. Until September 2012, 21 mo after ETV discontinuation, his HBsAg level remained negative and the patient’s anti-HBs titer had increased to 112.3 mIU/mL (Figure 2). His ALT levels also remained normal, while the HBV DNA concentration was undetectable at the patient’s last two visits (Figure 1). Administration of ETV was well tolerated throughout the treatment period.

Other reported cases

The nucleoside analog ETV provides the advantage of a higher genetic barrier to resistance than LAM for the treatment of chronic hepatitis B[9]. ETV has also been used to prevent HBV reactivation during chemotherapy or immunosuppressive therapy, although this experience is limited[10]. Several studies have examined the use of ETV in the treatment of HBV reactivation in lymphoma patients and suggest its effectiveness and safety[11-13]. A total of 28 cases of HBV reactivation reported in the literature involved ETV administration during or after immunosuppressive chemotherapy in patients with lymphoma (Table 1). Nine cases of HBV reactivation developed during chemotherapy or immunotherapy[11,17], while the remaining cases occurred after chemotherapy or immunotherapy[11,14,18-22]. Twenty-four patients received rituximab-based immunotherapy regimens[12-22]. Five patients died of hepatic failure following HBV reactivation[11,15,17,20,22]. Of these, 3 developed HBV reactivation-related hepatitis 2-4 mo after discontinuation of LAM while the remaining case of HBV reactivation occurred 8 mo after cessation of LAM treatment[11].

DISCUSSION

Malignant lymphoma is a leading cause of cancer-related
HBsAg: Hepatitis B surface antigen; HBsAg: Hepatitis B surface antigen.

Figure 1 Time course of serum hepatitis B virus DNA and alanine aminotransferase levels during and after immunochemotherapy. HBsAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase.

Figure 2 Time course of quantitative titers of hepatitis B surface antigen and hepatitis B surface antibody antibodies after entecavir treatment. Anti-HBs: Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen.

mortality, despite the fact that the long-term prognosis of patients with diffuse large B cell lymphoma has improved following the introduction of immunochemo-

therapeutic agents, such as rituximab[21]. In addition, reactivation of HBV may be a fatal complication in patients with HBV infection who receive immunotherapy for lymphoma, especially rituximab-based regimens. While the exact definition of HBV reactivation differs among investigators[23], reactivation of HBV is deemed to occur in both HBsAg-positive or -negative patients. Among patients who only present with anti-HBc antibody-positive serology, the risk factors for HBV reactivation include male gender and low anti-HBc titer[14].

Given the substantial morbidity and mortality associated with HBV reactivation and hepatitis flares, prophylactic antiviral therapy should be administered to HBsAg-positive cancer patients if they receive immunochemotherapy. LAM has been shown to be clinically effective in reducing the incidence and severity of HBV reactivation, but treatment guidelines differ in their recommendations for prophylactic antiviral therapy[26-28]. In addition, the optimal duration of prophylactic LAM therapy has not yet been clearly established. For instance, the incidence of YMDD mutation and HBV reactivation following withdrawal of LAM in patients with NHL were similar to that for patients with chronic hepatitis B. In a long-term study, 17% of HBsAg-positive NHL patients developed YMDD mutation during LAM therapy (median duration: 11.5 mo), and 4% developed HBV reactivation following LAM withdrawal[29]. In one prospective study, 23.9% of 46 patients with hematological malignancies developed HBV reactivation after withdrawal of LAM prophylaxis[30]. HBV reactivation was more likely to develop in patients with elevated HBV DNA levels prior to chemotherapy. A prolonged administration of antiviral therapy may be necessary in these patients; however, drug resistance must be considered. ETV may be the preferred drug because ofits high antiviral potency and high barrier to resistance. In a retrospective study, ETV showed a very low rate of prophylaxis failure. HBV reactivation was not detected in 31 HBsAg-positive patients treated with ETV prophylaxis (median duration: 17 mo)[31]. A randomized controlled trial confirmed that ETV prophylaxis until 3 mo after completion of chemotherapy was insufficient even in patients with undetectable hepatitis B. One of the 41 patients in the ETV prophylaxis group had delayed HBV reactivation, almost 7 mo after discontinuing ETV prophylaxis. Therefore, it is important to routinely monitor HBV DNA levels after discontinuation of ETV[32].

In conclusion, prophylactic antiviral therapy is highly recommended in patients with active or occult HBV infection who receive chemotherapy or immunotherapy. In the event of HBV reactivation at the time HBV prophylaxis is stopped, administration of a potent antiviral agent with a high genetic barrier to resistance should be considered.

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COMMENTS

Case characteristics
A 68-year-old patient was admitted to hospital for follicular lymphoma, with a 2-decade history of chronic hepatitis B virus (HBV) infection. He received rituximab-based immunotherapy for follicular lymphoma and experienced HBV reactivation following cessation of lamivudine prophylaxis.

Clinical diagnosis
The patient had no symptoms or signs when HBV reactivation occurred.

Differential diagnosis
Hepatitis due to drugs, alcoholic hepatitis, and other factors were excluded.

Laboratory diagnosis
After cessation of lamivudine (LAM) prophylaxis, the patient's HBV DNA (by polymerase chain reaction) rose to 8.15 × 10^6 copies/mL from an undetectable baseline level, followed by elevated alanine aminotransferase.

Treatment
The patient received entecavir (ETV) 0.5 mg/d for 10 mo and experienced sustained viral suppression with HBsAg seroconversion.

Related reports
ETV provides the advantage of a higher genetic barrier to resistance than LAM for the treatment of chronic hepatitis B. Several studies examining the use of ETV for treating HBV reactivation in lymphoma patients suggest that it is a safe and effective therapy.

Term explanation
HBV reactivation was defined as a tenfold increase in HBV DNA level or the reappearance of detectable HBV DNA.

Experience and lessons
Prophylactic antiviral therapy is highly recommended in patients with active or occult HBV infection who receive chemotherapy or immunotherapy; a potent antiviral agent with a high genetic barrier to resistance should be considered. Peer review
This case report the relatively uncommon finding of hepatitis B surface antigen seroconversion following ETV therapy in a lymphoma patient with chronic HBV who experienced HBV reactivation following rituximab-based immunotherapy. It is well written.

REFERENCES
1. Nath A, Agarwal R, Malhotra P, Varma S. Prevalence of hepatitis B virus infection in non-Hodgkin lymphoma: a systematic review and meta-analysis. Intern Med J 2010; 40: 633-641 [PMID: 19811561 DOI: 10.1111/j.1445-5994.2009.02860]
2. Michielsen P, Ho E. Viral hepatitis B and hepatocellular carcinoma. Acta Gastroenterol Belg 2011; 74: 4-8 [PMID: 21563647]
3. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, Lefort S, Marit G, Macro M, Sebban C, Belhadj K, Bordessoule D, Ferme C, Tilly H. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d’Etudes des Lymphomes de l’Adulte. Blood 2010; 116: 2040-2045 [PMID: 20548096 DOI: 10.1182/blood-2010-03-276246]
4. Freundschuh M, Kuhn H, Trümper L, Osterborg A, Trneny M, Shepherd L, Gill DS, Walowski J, Pettingell R, Jaeger U, Zinzani PL, Shpilberg O, Kvaloy S, de Nully Brown P, Stahel R, Milpied N, López-Guillermo A, Poeschel V, Grass S, Loefler M, Murawski N. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study for the MabThera International Trial (MInT) Group. Lancet Oncol 2011; 12: 1013-1022 [PMID: 21940214 DOI: 10.1016/S1470-2045(11)70235-2]
5. Mastroianni CM, Lichtner M, Cleton R, Del Borgo C, Rago A, Martini H, Cimino G, Vullo V. Current trends in management of hepatitis B virus reactivation in the biologic therapy
Hepatitis B virus infection is a major global health concern, with an estimated 240 million chronic carriers worldwide. The management of hepatitis B virus infection is complex and requires a multidisciplinary approach. In patients with hematological malignancies, the use of rituximab-containing regimens has led to increased risk of hepatitis B virus reactivation. This has necessitated the implementation of antiviral prophylaxis to prevent disease progression. Various antiviral agents, such as entecavir and tenofovir, have been shown to be effective in preventing hepatitis B virus reactivation in rituximab-treated patients.

Wong GL, Yiu KK, Chim AM, Chu SH, Chan McMahon BJ. Chronic hepatitis B: update 2009. J Clin Virol 2010; 50: 171-179 [PMID: 20665280 DOI: 10.1016/j.jcv.2010.05.004]

Wong VW, Wong GL, Yiu KK, Chim AM, Chu SH, Chan McMahon BJ. Chronic hepatitis B: update 2009. J Clin Virol 2010; 50: 171-179 [PMID: 20665280 DOI: 10.1016/j.jcv.2010.05.004]
Liu WP et al. HBV recurrence and HBsAg seroconversion in NHL

2765-2772 [PMID: 23775967 DOI: 10.1200/JCO.2012.48.5938]

33 Liu J, Yang HI, Lee MH, Lu SN, Jen CL, Wang LY, You SL, Iloeje UH, Chen CJ. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. Gastroenterology 2010; 139: 474-482 [PMID: 20434450 DOI: 10.1053/j.gastro.2010.04.048]

34 Yang HI, Hung HL, Lee MH, Liu J, Jen CL, Su J, Wang LY, Lu SN, You SL, Iloeje UH, Chen CJ. Incidence and determinants of spontaneous seroclearance of hepatitis B e antigen and DNA in patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2012; 10: 527-534.e1-2 [PMID: 22179461 DOI: 10.1016/j.cgh.2011.12.019]

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