Hepatitis B Virus Reactivation After 23 Months of Rituximab-based Chemotherapy in an HBsAg-negative, Anti-HBs-positive Patient With Follicular Lymphoma

I-Cheng Lee[1], Yi-Hsiang Huang[1,2]*, Chi-Jen Chu[1], Pui-Ching Lee[1], Han-Chieh Lin[1], Shou-Dong Lee[1]

[1]Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, and [2]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

A 72-year-old female negative for hepatitis B surface antigen (HBsAg) and positive for antibody to hepatitis B surface antigen (anti-HBs) was diagnosed to have follicular lymphoma in 2006. Seventeen cycles of rituximab-based chemotherapy were administered over 23 months. Twelve days after the last cycle of chemotherapy, serum aminotransferase levels were elevated, and hepatitis serology tests revealed reappearance of HBsAg and hepatitis B e antigen (HBeAg), loss of anti-HBs, and positivity for hepatitis B virus (HBV) DNA. Antiviral treatment with entecavir was administered immediately, and the hepatitis flare was controlled. Rituximab-based chemotherapy can induce HBV reactivation even in HBsAg-negative, anti-HBs-positive patients. Early recognition and prompt antiviral treatment is crucial for patients with HBV reactivation during anticancer therapy. [*J Chin Med Assoc* 2010;73(3):156–160]

Key Words: anti-HBc positive, chemotherapy, HBV reactivation, non-Hodgkin's lymphoma, rituximab

Introduction

Chronic hepatitis B is prevalent in Asia and Taiwan, and a major cause of liver-related morbidity and mortality.[1] Hepatitis B virus (HBV) reactivation is a well-recognized complication in HBV carriers undergoing cancer chemotherapy.[2] Patients with occult HBV infection, who are negative for hepatitis B surface antigen (HBsAg), positive for antibody to hepatitis B core antigen (anti-HBc) and positive for HBV DNA, also carry the risk of HBV reactivation during chemotherapy, especially in lymphoma patients.[3] Current guidelines for chronic hepatitis B suggest the use of prophylactic antiviral therapy for HBsAg-positive patients at the onset of chemotherapy.[4] Rituximab, a chimeric monoclonal antibody against the protein CD20, is the standard treatment for CD20-positive non-Hodgkin's lymphoma (NHL).[5–7] HBV reactivation and progression to fatal hepatic failure has been increasingly observed in NHL patients with HBV infection (Table 1).[8–19] The presence of antibody to hepatitis B surface antigen (anti-HBs) has been identified to be a factor to prevent HBV reactivation in patients with occult HBV infection receiving chemotherapy. In previous reports, most of the patients were negative for anti-HBs.[8] Here, we report a case of reappearance of HBsAg and hepatitis B e antigen (HBeAg) after 23 months of rituximab-based immunochemotherapy in a HBsAg-negative and anti-HBs-positive follicular lymphoma patient. Monitoring liver function and early administration of antiviral agents when reactivation of hepatitis B is recognized can successfully prevent further progression of hepatitis B.

Case Report

A 72-year-old female patient was diagnosed with follicular lymphoma, stage IV, by bone marrow biopsy and computed tomography in January 2006. The tumor involved the bone marrow, bilateral axillary, supraclavicular, mediastinal, intra-abdominal and retroperitoneal lymph nodes, with initial presentation of a

*Correspondence to: Dr Yi-Hsiang Huang, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: yhhuang@vghtpe.gov.tw • Received: June 30, 2009 • Accepted: December 23, 2009

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Table 1. Reports of HBV reactivation in HBsAg-negative lymphoma patients receiving rituximab-based chemotherapy

Reference	Age (yr)	Sex	Diagnosis	Chemotherapy regimen	Pretreatment HBV markers	Time of HBV reactivation after starting rituximab	Peak ALT (U/L)	Treatment	Outcome
Dervite et al, 2001[9]	73	M	FL	R + CHOP + IFN + ARA-C	Anti-HBs +	6 mo	1,230	Supportive	Persistent HbsAg +
Westhoff et al, 2003[10]	73	M	DLBCL	R	Anti-HBs + , anti-HBc +	3 mo	NR	Lamivudine	Died of hepatic failure
Tsutsumi et al, 2004[11] ($n = 2$)	55	M	DLBCL	R + C + Ara-C + VP16 + Dex	Anti-HBs + , anti-HBe +	2 cycles	84	Supportive	Resolved
	80	M	DLBCL	R + O	Anti-HBs + , anti-HBe +	3 cycles	101	Supportive	Resolved
Sarrecchia et al, 2005[12]	53	M	CLL	R	Anti-HBs + , anti-HBc +	3 mo	2,120	Lamivudine	Died of hepatic failure
Law et al, 2005[13]	67	M	NHL	R-CHOP	Anti-HBs + , anti-HBc +	8 cycles	2,240	Lamivudine	Died of hepatic failure
Niscola et al, 2005[14]	51	M	CLL	R	Anti-HBs –, anti-HBc +	7 mo	NR	Lamivudine	Died of hepatic failure
Sera et al, 2006[15]	59	M	NHL	R + VP16 + P + Dex	Anti-HBs +, anti-HBc +	2 mo	359	Lamivudine	Died of hepatic failure
Ozgonenel et al, 2006[16]	21	M	DLBCL	R-CHOP	Unknown	3 cycles	NR	Lamivudine	Died of hepatic failure
Yamagata et al, 2007[17]	54	M	DLBCL	R-CHOP	Anti-HBc +	7 cycles	531	Lamivudine	Died of hepatic failure
Dillon et al, 2008[18]	21	F	MLBCL	R-CHOP	Unknown	4 mo	> 400	Lamivudine	Died of hepatic failure
Yeo et al, 2009[8] ($n = 5$)	77	M	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	7 mo	2,110	Lamivudine	Died of hepatic failure
	58	M	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	5 cycles	362	Lamivudine	Resolved
	60	M	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	9 mo	3,499	Supportive	Resolved
	63	M	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	7 mo	649	Lamivudine	Resolved
	46	M	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	10 mo	809	Lamivudine	Died of lymphoma
Wu et al, 2009[19]	52	F	DLBCL	R-CHOP	Anti-HBs –, anti-HBc +	6 mo	765	Lamivudine	Died of hepatic failure

HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; ALT = alanine aminotransferase; FL = follicular lymphoma; DLBCL = diffuse large B cell lymphoma; CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin's lymphoma; MLBCL = mediastinal large B cell lymphoma; R = rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; IFN = interferon; ARA-C = cytarabine; C = cyclophosphamide; VP16 = etoposide; Dex = dexamethasone; O = vincristine; P = prednisolone; anti-HBs = antibody to hepatitis B surface antigen; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; NR = not reported.

palpable solid mass in the neck. Virologic markers were negative for HBsAg, and positive for anti-HBs before chemotherapy.

Chemotherapy with R-OP (rituximab, vincristine, prednisolone) was started on May 3, 2006, and was completed on April 29, 2007, for a total of 9 cycles. Then, a course of R-COP (rituximab, cyclophosphamide, vincristine, prednisolone) was administered on August 15, 2007. Due to unsatisfactory response, augmented chemotherapy regimen with R-CHOP (rituximab, cyclophosphamide, pegylated liposomal doxorubicin, vincristine, prednisolone) was started in September 2007, and completed in January 2008, for a total of 6 cycles. Another course of R-OP was administered on April 10, 2008.

Reduction in tumor size was documented on follow-up computed tomography. Liver function tests had been regularly monitored; there was no elevation of serum aminotransferase levels throughout the courses of chemotherapy. However, hepatitis flares with alanine aminotransferase >2 times the upper limit of normal (119 U/L) was noted on April 22, 2008 (Figure 1). Virologic markers were positive for HBsAg and HBeAg, and there was disappearance of anti-HBs. HBV DNA tests revealed a high HBV viral load (1.71×10^9 copies/mL). Antiviral therapy with entecavir 0.5 mg daily was started immediately. Aminotransferase levels declined, and no hepatic decompensation developed thereafter. HBV DNA tests at 1 month, 3 months and 12 months after antiviral therapy were 1.71×10^9, 9.71×10^6 and 2,880 copies/mL, respectively. The patient is alive, and the tumor is in stable disease status.

Discussion

Current AASLD (American Association for the Study of Liver Diseases) and APASL (Asian Pacific Association for the Study of the Liver) guidelines recommend routine HBsAg testing for patients at high risk for HBV infection before the initiation of chemotherapy, and prophylactic antiviral therapy should be administered to hepatitis B carriers at the onset of chemotherapy and maintained for 3–6 months afterwards.[4,20] In contrast, the incidence of HBV reactivation in patients with resolved infection who are HBsAg-negative, anti-HBs-positive and anti-HBc-positive has been much lower, and routine prophylactic antiviral treatment is not mandatory. In recent years, the incorporation of rituximab into the standard CHOP chemotherapy regimen for CD20-positive NHL has been shown to improve clinical outcomes.[5] However, HBV reactivation in this population has been increasingly reported. Yeo et al reported that HBV reactivation developed in a high proportion of lymphoma patients with occult HBV infection undergoing rituximab-based chemotherapy.[8] Among 21 diffuse large B cell lymphoma patients who were HBsAg-negative and anti-HBc-positive, 5 patients developed HBV reactivation after receiving

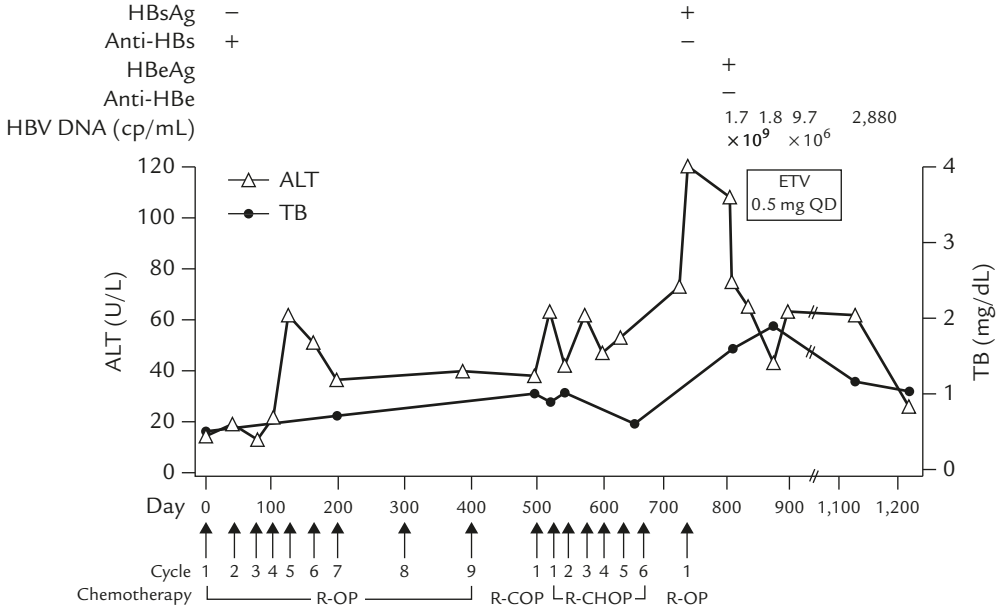

Figure 1. Serum alanine aminotransferase (ALT) and total bilirubin (TB) levels during and after rituximab-based chemotherapy. Entecavir (ETV) 0.5 mg/day was initiated on day 806. R-OP = rituximab, vincristine, and prednisolone; R-COP = rituximab, cyclophosphamide, vincristine, and prednisolone; R-CHOP = rituximab, cyclophosphamide, pegylated liposomal doxorubicin, vincristine, and prednisolone.

R-CHOP chemotherapy, including 1 patient who died of hepatic failure. These 5 patients with HBV reactivation were all negative for anti-HBs. In contrast, none of the patients who were HBsAg-negative and anti-HBc-positive developed HBV reactivation after receiving CHOP alone. Male sex, absence of anti-HBs, and use of rituximab were factors associated with HBV reactivation. Therefore, the risk of HBV reactivation in patients with occult HBV infection could be stratified according to the serologic profile of patients and the chemotherapy regimen. The risk is further increased in the absence of anti-HBs during rituximab-based chemotherapy.

Reactivation of HBV infection was studied in 626 Hong Kong patients with cancer who received cytotoxic chemotherapy over a 12-month period.[21] Of these patients with chronic HBV infection under chemotherapy, HBV reactivation occurred in nearly 20%. Reactivation was more likely to develop in patients who were male, of younger age, HBeAg-negative, and diagnosed with lymphoma. A recent study from Singapore showed an association between the presence of NHL and HBV reactivation.[22] The prevalence rate of HBV infection in the study group was 10.3%, significantly higher than the prevalence rate of 4.1% in the general population. The high mortality rate of rituximab-related HBV reactivation was reported in a recent study.[23] Among the patients with HBV reactivation after rituximab treatment, 52% (13 of 25 patients) died due to hepatic failure.

In our anti-HBs-positive case, due to the indolent nature of follicular lymphoma, a total of 17 cycles of rituximab-based chemotherapy was administered in 23 months (from May 2006 to April 2008), and HBV reactivation eventually developed. The association of duration of rituximab treatment and HBV reactivation has not been well clarified. In previous reports of HBV reactivation in HBsAg-negative, anti-HBc-positive lymphoma patients after rituximab treatment, the time of HBV reactivation ranged from the 2nd to the 8th course of anticancer therapy.[8–19] Wu et al recently reported a case of fatal HBV reactivation after R-CHOP chemotherapy.[19] In their report, fatal HBV reactivation developed after 6 cycles of R-CHOP chemotherapy despite immediate administration of antiviral therapy. In contrast, close monitoring of serum aminotransferase levels, early recognition of HBV reactivation, and prompt antiviral therapy in our patient resulted in suppression of HBV DNA levels, normalization of liver function, and avoidance of hepatic failure.

In HBsAg-positive lymphoma patients receiving cytotoxic chemotherapy, clinical studies have shown that prophylactic therapy with lamivudine could reduce the risk of HBV reactivation, severity of hepatitis flares, and mortality.[2,24,25] Currently, there is no suggestion for prophylactic antiviral therapy in HBsAg-negative, anti-HBc-positive lymphoma patients undergoing chemotherapy. However, there have been many cases to date in which hepatic failure occurred despite administration of lamivudine after recognition of HBV reactivation, presumably due to the relative delay in the start of antiviral therapy.[6] HBV reactivation is defined as an increase in HBV DNA level of $>1\log_{10}$ IU/mL.[26] Therefore, we suggest screening HBV status, including HBsAg, anti-HBs, and anti-HBc, for all patients before they receive rituximab-based chemotherapy, and HBV DNA should be tested if anti-HBc is positive. Because HBV reactivation may develop within as few as 2 cycles of chemotherapy, HBV DNA should be rechecked after 2 cycles of rituximab-based chemotherapy in anti-HBc-positive patients, and antiviral treatment should be started as soon as HBV DNA has increased 10-fold compared to baseline, and $>2{,}000$ IU/mL.

In conclusion, screening of HBV status for all patients before they receive chemotherapy is important, including HBsAg, anti-HBs, and anti-HBc. Regular HBV DNA monitoring and prophylactic antiviral therapy are highly recommended if there is evidence of active or occult HBV infection.

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