INTRODUCTION

Although vaccination for the prevention of hepatitis B virus (HBV) infection has been effectively used for over 25 years, HBV infection is still one of the most important and fatal infectious liver diseases, with approximately 400 million chronically infected people worldwide. The prevalence of chronic HBV infection in developed countries such as Western Europe and the USA is currently less than 1-2%, however in Asia, Africa, and some Mediterranean countries, the prevalence exceeds as high as 10%. Above all, in these high prevalence areas, past or remote HBV infection as well as overt HBV infection may cause serious health problems.

Background/Aims: The widespread use of cytotoxic chemotherapy and immunosuppressants has resulted in reactivation of hepatitis B virus (HBV) recently becoming an issue. Although rituximab (an anti-CD20 monoclonal antibody) has revolutionized the treatment of lymphoma, recent reports have suggested that rituximab therapy increases the risk of viral-mediated complications, and particularly HBV reactivation. This study analyzed real clinical practice data for rituximab-related HBV reactivation.

Methods: Between January 2005 and December 2011, 169 patients received treatment with rituximab. Screening status of the HBV infection and frequency of preemptive therapy were determined in these patients, and the clinical features of HBV reactivation were analyzed.

Results: Seventy-nine of the 169 patients with chronic or past HBV infection were selected for evaluation of HBV reactivation. Of the 90 patients who were excluded, 22 (13.0%) were not assessed for HBsAg and anti-HBc, and 14 (8.3%) were not assessed for anti-HBc due to seronegativity for HBsAg. The selected patients were divided into those with chronic HBV infection (n=12) and those with past HBV infection (n=67); six patients (7.6%) experienced HBV reactivation. Eight patients received preemptive therapy, but three patients (37.5%) underwent HBV reactivation. Although HBsAg seropositivity was an independent risk factor for HBV reactivation (P=0.038), of the six patients with HBV reactivation, two (33.3%) had past HBV infection and three (50%) died of liver failure.

Conclusions: The findings of this study demonstrate that adherence to guidelines for screening and preemptive therapy for HBV reactivation was negligent among the included cohort. Attention should be paid to HBV reactivation in patients with past as well as chronic HBV infection during and after rituximab therapy. (Clin Mol Hepatol 2013;19:51-59)

Keywords: Hepatitis B virus; Immunosuppressant; Rituximab

Abbreviations:
HBV, hepatitis B virus; FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to HBsAg; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; anti-HBc, antibody to hepatitis B core; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PT, prothrombin time; PCR, polymerase chain reaction; HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval; cccDNA, covalently closed circular DNA; GRE, glucocorticoid responsive element

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Recently, with wide-spread use of cytotoxic chemotherapy or immunosuppressants such as high-dose corticosteroids and biologic agents, reactivation of HBV is becoming an issue. Because the goal of newly invented drugs is mostly to control human immune system, this issue becomes more important. In particular, rituximab is a human/murine chimeric monoclonal antibody directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes. It was approved by the U.S. Food and Drug Administration (FDA) in 2006, primarily for the treatment of B-cell malignancies such as non-Hodgkin’s lymphomas. Since then, its use has expanded to the treatment of many other diseases, including rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, Sjögren’s syndrome, multiple sclerosis, graft vs. host disease, autoimmune hepatitis, and dermatomyositis.

Several reports have suggested that rituximab therapy may increase the risk of viral-mediated complications, particularly HBV reactivation. HBV reactivation associated with rituximab therapy is usually subclinical, however, frequently it can result in the development of severe complications, including acute liver failure and death. In October 2004, the U.S. FDA reported that the use of rituximab might be associated with episodes of fulminant hepatitis. In endemic areas such as Korea, Taiwan and China, there are many patients with current or past HBV infection. Therefore, reactivation of HBV induced by rituximab therapy can be a serious clinical problem in these areas. The aim of this study was to inquire the actual condition of preparation for HBV reactivation prior to rituximab therapy in clinical practice, and to investigate clinical features and risk factors for HBV reactivation during or after rituximab-based therapy at a single tertiary institute in an area with a high prevalence of HBV infection.

MATERIALS AND METHODS

From January 2005 to December 2011, a total of 169 patients received treatment with rituximab at Yeungnam University hospital. The subjects for this study were selected regardless of treatment departments. All medical records were retrospectively reviewed. Of 169 patients, 79 patients with chronic HBV infection or past HBV infection were selected for evaluation of HBV reactivation in this study. The demographic characteristics of the patients, the incidence of HBV reactivation and its risk factors in association with rituximab therapy were analyzed. Assessments of the frequency and results for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), antibodies to hepatitis B core (anti-HBc), serum alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), prothrombin time (PT), white blood cell, hemoglobin, platelet and HBV DNA polymerase chain reaction (PCR) were performed for all patients before or during rituximab therapy. The HBV DNA load was measured by quantitative real-time PCR assay (Cobas Taqman HBV-DNA Test, Roche Diagnostics Systems, CA, USA) with a minimal sensitivity of 20 IU/mL. Measurement of HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe was performed using commercially available enzyme immunoassays (Architect i2000SR, Abbott Diagnostics, IL, USA). We calculated the total dose and the mean dose per cycle of rituximab. This study was conducted in accordance with the Helsinki Declaration. The medical ethical committee of our medical center approved the study protocol.

Definition

HBV reactivation and hepatitis were defined as follows. HBV reactivation was defined as reappearance or an increase in serum HBV DNA over 10 folds (1 log_{10} IU/mL), compared with the pretreatment level. Hepatitis was defined as a threefold or greater increase in serum ALT level that exceeded 120 IU/L (reference range, <40 IU/L). Chronic HBV infection was defined as HBsAg seropositivity over a period of six months, irrespective of HBeAg and HBV DNA seropositivity, including chronic inactive carriers. Past or resolved HBV infection was defined as HBsAg and HBV DNA seronegative, anti-HBc seropositive, and/or anti-HBs seropositive. Liver cirrhosis was defined by histologic, clinical or radiological evidence. Clinical signs of liver cirrhosis included lower platelet count (<1.4×10^{12} cell/μL), the existence of varix, or the development of ascites. Patients with fever or hypothermia, leukocytosis or leukopenia, tachypnea, tachycardia, with a proven or suspected infectious condition, were regarded as having sepsis. Preemptive antiviral therapy was defined as the administration of an antiviral agent prior to the start of rituximab therapy.

Statistical analysis

Quantitative data were presented as the mean value ± standard deviation (range). The independent-samples t test was used if parametric assumptions were met for numerical data. Mann-Whitney U test was used when parametric assumptions were not met. For categorical measures, Pearson χ^2 or Fisher’s exact tests.