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Prophylaxis of Hepatitis B Reactivation Using Lamivudine in a Patient Receiving Rituximab

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A 53-year-old man who had a history of fluminant hepatitis caused by precore mutant hepatitis B virus (HBV) was admitted to our hospital for the treatment of relapsed non-Hodgkin's lymphoma in July 2000. At admission, serum levels of aspartate aminotransferase and alanine aminotransferase were normal, but he tested positive for HBs antigen. The titer was 64-fold by radioimmunoassay. We initiated lamivudine at a daily dose of 75 mg to prevent HBV proliferation during chemotherapy. By September 2000, he had received six courses of rituximab at 375 mg/m^2 and four courses of fludarabine and mitoxantrone. No hepatic damage was observed from the initiation of treatment until March 2001. At present, four months after the completion of chemotherapy, he continues lamivudine, and the titer of HBs antigen is low at 4-fold. Rituximab is usually associated with mild toxicity, usually limited to infusion periods. The drug is not generally associated with increased incidence of opportunistic infections. However, some case reports have been recently published on severe viral infections following administration of rituximab. These include fluminant hepatitis caused by HBV, pure red cell aplasia due to parvovirus B19 and fatal varicella-zoster infection. While it remains unknown whether rituximab can be safely administered in patients with chronic HBV infection, this case report suggested that prophylactic administration of lamivudine is beneficial for suppressing reactivation of HBV during chemotherapy including rituximab. Rituximab should be used cautiously for patients with HBV infection, but prophylactic administration of lamivudine may be beneficial for preventing reactivation of HBV. Am. J. Hematol. 68:292–294, 2001.

Key words: hepatitis B virus; rituximab; lamivudine; non-Hodgkin's lymphoma

INTRODUCTION

Rituximab is used for the treatment of malignant lymphoma expressing CD20 antigen [1,2]. Its toxicity is generally mild and is usually limited to infusion periods. While the drug temporarily eliminates normal B-lymphocytes expressing CD20, it is not generally associated with increased incidence of opportunistic infections [3]. Normal B-lymphocytes re-emerge weeks to months after administration of rituximab, and antibody production continues during B lymphocytopenia because plasma cells do not express CD20. However, Derivite et al. recently reported a patient with latent hepatitis B virus (HBV) infection who developed severe acute hepatitis following administration of rituximab [4]. Furthermore, viral infections such as pure red cell aplasia due to parvovirus B19 and fatal varicella-zoster infection have been reported following administration of rituximab [5,6]. At present, it remains unknown whether rituximab can be safely administered in patients with chronic HBV infection. We experienced a patient with HBV precore mutant infection, in whom rituximab was administered without reactivation of HBV, using prophylactic administration of lamivudine. A detailed

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description of his clinical course provides important information on the management of HBV infection in patients receiving rituximab.

CASE

A 53-year-old man was diagnosed as having stage IV follicular non-Hodgkin's lymphoma in January 1994. HBs antigen and HBe antibody were positive, and HBs antibody and HBe antigen were negative. The patient tested positive for HBV precore mutant. The titer of HBs antibody was 32-fold using radioimmunoassay. He received combination chemotherapy consisting of cyclophosphamide, vincristine, and adriamycin. Because of the possible risk of HBV reactivation, corticosteroid was not administered. Six courses of combination chemotherapy were completed in April 1994. Response to the treatment was poor, and generalized lymphadenopathy persisted. In May 1994, he developed malaise and jaundice. He was readmitted to our hospital. Jaundice and hepatomegaly were evident on the initial examination. Serum levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin were elevated to 5634 IU/L, 4412 IU/L, and 6.8 mg/dL, respectively. The titer of HBs antigen was 2048-fold. Exacerbation of chronic active hepatitis B was diagnosed. He responded to conventional treatment for acute liver failure including corticosteroid, glucagon and insulin, and plasma exchange, and his hepatic function normalized after a month of treatment. Corticosteroid was tapered slowly to prevent recurrence of HBV infection. He did not receive any cytotoxic agents until July 2000, when the lymphoma progressed. He was admitted to our hospital in July 2000, when serum levels of aspartate aminotransferase and alanine aminotransferase were normal, but he tested positive for HBs antigen. The titer was 64-fold. We initiated lamivudine at a daily dose of 75 mg to prevent HBV proliferation during chemotherapy. By September 2000, he had received six courses of rituximab at 375 mg/m^2 and four courses of fludarabine and mitoxantrone. No hepatic damage was observed from the initiation of treatment until now, March 2001. At present, four months after the completion of chemotherapy, he continues lamivudine, and the titer of HBs antigen is low at 4-fold.

DISCUSSION

Reactivation of HBV replication is a well-known complication in patients with chronic HBV infection receiving cytotoxic or immunosuppressive therapy [7]. Especially, HBV precore mutant is a risk factor for fluminant hepatitis in patients receiving immunosuppressive agents [8]. This patient was a carrier of precore mutant HBV, and had a history of severe hepatitis during cytotoxic chemotherapy. He was therefore at a high risk of HBV reactivation during chemotherapy including rituximab, fludarabine, and mitoxantrone. As a case of fatal hepatitis following rituximab treatment was recently reported [4], combination chemotherapy might lead to reactivation of HBV by transiently decreasing antibodies against HBV antigens. We therefore used lamivudine as prophylaxis against HBV reactivation. Lamivudine, an inhibitor of HBV reverse transcriptase, is reported to reduce serum HBV DNA in patients receiving chemotherapeutic agents [9,10]. We considered that the drug might be useful for preventing fatal HBV hepatitis following rituximab therapy. As we expected, HBs antigen did not increase during and after chemotherapy in this patient. These findings suggested that prophylactic administration of lamivudine was successful in suppressing reactivation of HBV during chemotherapy including rituximab. We consider that rituximab should be used cautiously for patients with HBV infection, but prophylactic administration of lamivudine may be beneficial for preventing reactivation of HBV.

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