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Short Communication

Hepatitis B Reactivation in a Multiple Myeloma Patient with Resolved Hepatitis B Infection during Bortezomib Therapy : Case Report

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It has recently been reported that hepatitis B virus (HBV) reactivation in patients with hepatitis B surface antigen (HBsAg)-negative lymphoma during or after cytotoxic therapy occurs after the use of rituximab and stem cell transplantation for hematologic malignancies. However, clinical data on HBV reactivation in multiple myeloma patients have not been extensively reported. This is the first reported case of HBV reactivation in an HBsAg-negative myeloma patient treated with bortezomib (BOR) as salvage therapy and not stem cell transplantation. By closely monitoring HBV-DNA and early administration of entecavir, severe hepatitis was avoided and BOR therapy was continued. We suggest the importance of close monitoring of HBV-DNA for transplant-ineligible myeloma patients treated with BOR as salvage therapy. 〔*J Clin Exp Hematopathol 52(1) : 67-69, 2012*〕

Keywords: hepatitis B virus reactivation, multiple myeloma, bortezomib, entecavir

INTRODUCTION

Reactivation of hepatitis B virus (HBV) infection is a well-recognized complication in cancer patients with chronic HBV (hepatitis B surface antigen [HBsAg]-positive) undergoing cytotoxic chemotherapy, and prophylactic antiviral therapy before chemotherapy is recommended in such individuals.[1,2] After the use of rituximab and stem cell transplantation for hematologic malignancies, HBV reactivation in patients with resolved HBV infection (HBsAg-negative and HBs antibody [anti-HBs]-positive and/or hepatitis B core antibody [anti-HBc]-positive) during or after cytotoxic therapy has been recently reported.[1-5] Among lymphoma patients with resolved HBV infection treated with chemotherapy containing rituximab, 25% developed HBV reactivation.[4] One-quarter of this group of 25% developed fulminant hepatic failure with an extremely high mortality rate.[5] Clinical data on HBV reactivation in multiple myeloma (MM) patients have not been extensively reported. Some reports described HBV reactivation in myeloma patients with resolved HBV infection, but most studies reported HBV reactivation after autologous stem cell transplantation (ASCT).[6-8]

We report a case of HBV reactivation in a myeloma patient with resolved HBV infection during bortezomib (BOR) treatment as salvage therapy and successful management with close monitoring of HBV-DNA as well as early administration of entecavir (ETV).

CASE REPORT

A 72-year-old Japanese male who underwent a gastrectomy due to gastric ulcers at age 50 was diagnosed with monoclonal gammopathy of undetermined significance (MGUS) (IgG-κ, Bence-Jones protein-κ type) by a medical examination in 2005. He was regularly monitored without being given any therapy. However, MGUS transformed to symptomatic MM, and treatment (melphalan, prednisolone, and thalidomide) was started in October 2007. MM improved temporarily but became resistant to treatment, and anemia as well as renal disorders progressed. He was therefore admitted to our hospital for initiation of BOR therapy in January 2011.

Physical examination revealed no abnormal findings. Imaging demonstrated no extramedullary lesions or pathologi-

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cal fractures. Laboratory findings were as follows : white blood cell count, 5,800/μL without abnormal cells ; hemoglobin, 9.0 g/dL ; platelets, 168,000/μL ; total protein, 11.3 g/dL ; albumin, 2.5 g/dL ; creatinine, 1.27 mg/dL ; corrected calcium, 8.6 mg/dL ; IgG, 6,495 mg/dL ; IgA and IgM, < 10 mg/dL ; and β_2-microglobulin, 5.53 mg/L. Examination of bone marrow revealed 16.8% atypical plasma cells. Chromosomal analysis of bone marrow specimens using G-band staining was normal. Interphase fluorescence *in situ* hybridization studies revealed no deletion of 13q. He was seronegative for HBsAg and anti-HBc (0.46 and 0.63 [sample/cut-off ratio], respectively) and seropositive for anti-HBs (18.0 mIU/mL). Serum HBV-DNA was undetectable and the aminotranferase levels were normal.

He received a three-week cycle of BOR (1.0 mg/m^2) by intravenous bolus and DEXA (20 mg/body weight) on days 1, 4, 8, and 11. A trimethoprim-sulfamethoxazole combination and acyclovir were administered as prophylactic therapy. He suffered from peripheral sensory neuropathy ; mecobalamin and goshajinkigan were started and BOR and DEXA were reduced on days 1, 4, and 8 after the second course. A partial response was achieved before completing four courses. However, IgG levels increased gradually and DEXA increased on days 1, 2, 4, 5, 8, and 9 after eight courses without increase in BOR dosage. He had not received transfusion since BOR therapy started.

HBV-DNA was monitored monthly from the start of BOR therapy. After 10 courses of BOR therapy, HBV-DNA became detectable with up to 2.7 log copies/mL. Alanine aminotransferase (ALT) levels were almost in the normal range. BOR and DEXA were stopped and ETV (0.5 mg/day) was started. We observed that ALT levels did not increase for 3 weeks, and we resumed BOR and DEXA therapy (which consisted of BOR at 0.7 mg/m^2 and DEXA at 20 mg/body weight on days 1, 4, and 8). HBV-DNA was negative 4 weeks after ETV was started, and MM continued to exhibit a partial response.

DISCUSSION

BOR is a potent proteasome inhibitor that is currently used as therapy for myeloma.[9] It is associated with a significant risk of reactivation of infection by the varicella zoster virus,[10] and acyclovir prophylaxis is recommended.[11] One report stated that BOR suppresses HBV proliferation *in vitro*.[12] Two reports described HBV reactivation in patients receiving BOR therapy for myeloma. One study described a patient treated with BOR as salvage therapy after ASCT,[7] and another study described an HBsAg-positive patient discontinuing lamivudine prophylaxis.[13]

Ours is the first report of HBV reactivation in a myeloma patient with resolved HBV treated with BOR as salvage therapy and not ASCT. It is possible that fulminant hepatic failure might appear without close monitoring of HBV-DNA and early administration of ETV.

We administered a normal dose of BOR and DEXA to our patient. The myeloma was not refractory and a partial response was preserved. It is suggested that HBV reactivation can occur in other myeloma patients with resolved HBV infection treated with BOR as salvage therapy.

HBV reactivation in our patient developed immediately after increasing DEX. Steroid-containing regimen was shown not to be a risk factor for HBV reactivation in HBsAg-negative patients.[3] In HBsAg-positive patients, however, steroid was most frequently associated with HBV reactivation.[2]

It is important to check anti-HBs and anti-HBc as well as closely monitor HBV-DNA during BOR therapy even if a myeloma patient is HBsAg-negative and ineligible for ASCT. If HBV reactivation occurs, BOR therapy can be continued by closely monitoring HBV-DNA and by early administration of ETV.

REFERENCES

1 Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, *et al.*: Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 100:182-188, 1991

2 Yeo W, Johnson PJ: Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 43:209-220, 2006

3 Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, *et al.*: Kinetics and risk of *de novo* hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131:59-68, 2006

4 Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, *et al.*: Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 27:605-611, 2009

5 Umemura T, Tanaka E, Kiyosawa K, Kumada: Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. Clin Infect Dis 47:e52-56, 2008

6 Yoshida T, Kusumoto S, Inagaki A, Mori F, Ito A, *et al.*: Reactivation of hepatitis B virus in HBsAg-negative patients with multiple myeloma : two case reports. Int J Hematol 91:844-849, 2010

7 Mya DH, Han ST, Linn YC, Hwang WY, Goh YT, *et al.*: Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection. Ann Oncol 23:421-426, 2012

8 Uhm JE, Kim K, Lim TK, Park BB, Park S, *et al.*: Changes in serologic markers of hepatitis B following autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 13:463-468, 2007

9 Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, *et*

al.: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609-2617, 2003

10 Wu KL, van Wieringen W, Vellenga E, Zweegman S, Lokhorst HM, *et al*.: Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice. Haematologica 90:996-997, 2005

11 Vickrey E, Allen S, Mehta J, Singhal S: Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. Cancer 115:229-232, 2009

12 Bandi P, Garcia ML, Booth CJ, Chisari FV, Robek MD: Bortezomib inhibits hepatitis B virus replication in transgenic mice. Antimicrob Agents Chemother 54:749-756, 2010

13 Beysel S, Yegin ZA, Yagci M: Bortezomib-associated late hepatitis B reactivation in a case of multiple myeloma. Turk J Gastroenterol 21:197-198, 2010