Hepatocellular Carcinoma in a Patient with Chronic Hepatitis B Virus following the Treatment of Diffuse Large B-cell Lymphoma

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Hepatitis B virus (HBV) infection is major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in Korea. Even though the prevalence of HBV is decreasing due to nationwide vaccination, the rate of sero-positivity is still higher than that of western, especially in older age¹. Diffuse large B cell lymphoma (DLBCL) is curative disease with Rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy. High dose chemotherapy induces severe immunosuppression and can cause HBV viral reactivation, which can lead to develop substantial liver disease. Guidelines for the management of HBV carrier are recommended anti-viral prophylaxis before chemotherapy² to prevent viral reactivation. We present the case of a patient with a DLBCL in HBV carrier status and sequentially developed fatal HCC after R-CHOP chemotherapy.

Key Words: Hepatitis B; Lymphoma; Hepatocellular carcinoma

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is the common cause of hepatocellular carcinoma (HCC)³ and sero-positivity rate of Korean population is still higher than that of western countries¹. Diffuse large B cell lymphoma (DLBCL) is curative disease with Rituximab plus CHOP chemotherapy. The patient with HBV infection has a potential clinical relevancy accelerating the progression of the liver disease such as cirrhosis and HCC, especially in condition with severe immunosuppressed status, for example chemotherapy. Guidelines for the management of chronic HBV are recommended anti-viral prophylaxis for patients HBV before chemotherapy². We present the case of a patient with a DLBCL in HBV carrier status and sequentially developed fatal HCC after the administration of R-CHOP chemotherapy.

CASE

A 52-year-old male had been treated with six cycles of rituximab plus CHOP chemotherapy from February 2013 to June 2013 for a diffuse large B-cell lymphoma of stage IIA. Since he was known to be a chronic hepatitis B patient, he started telbivudine before starting chemotherapy. After he finished the three cycles of chemotherapy, he was achieved complete remission. According to the standard treatment protocol, he was received the additional three cycles of chemotherapy. He was checked up the last response evaluation on July 2013. Abdominal pelvic CT scan showed the newly appearing nodular lesion at liver dome, which was confirmed by hypermetabolic 2.4 cm mass lesion in Liver MRI and PET-CT scan (Fig. 1). Laboratory tests revealed: white blood cell count 3,100/uL, hemoglobin 10.9 g/dL, and platelet count 107,000/uL. The level of AST (33 IU/L), ALT (23 IU/L), bilirubin (0.53 mg/dL), alkaline phosphatase (116 IU/L), albumin (3.5 g/dL), and prothrombin time (11.3 sec) were within normal range. But, alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA II) were elevated to 358.8 ng/mL and 723
nAU/mL, respectively. He was diagnosed with hepatocellular carcinoma based on image studies and elevated tumor marker. The HBV viral load was increased to 1.19×106 copies/mL and HBV drug resistance mutation test showed telbivudine resistances (rtL180M and rtM204I) and anti-viral agent was changed to tenofovir. The patient was scheduled for surgery, but ICG R15 test result (24.4%) was not suitable for the segmentectomy. Instead, he was treated with TACE on August 2013. One month later, AFP and PIVKA-II were decreased to 240.8 ng/mL and 109 mAU/mL, respectively. On November 2013, follow up CT scan showed multiple liver mass, and lung and bone metastasis were newly observed. AFP was checked to 17,235.8 ng/mL. He was treated with sorafenib 800 mg from 19 November 2013 for palliative aim. After one month of using sorafenib, the patient was intolerable and his symptoms gradually worsened. In addition, CT scan results markedly deteriorated within a month, and AFP also rose to 56,277.4 ng/mL. Although the medical staff tried to treat with CAF, eventually he was died of pneumonia on 31 December 2013.

**DISCUSSION**

Several studies were published the relationships between hepatitis B viral infection and NHL (Non Hodgkin Lymphoma), but the result is still controversial. In 2007, US investigators brought out the results that chronic HBV carriers were 2.8 times more likely to develop NHL than matched comparison patients. However, Danish nationwide study revealed that the incidence of NHL was not higher in the HBV-infected cohort than non-infected cohort. In Korea, as hepatitis B endemic area, Kim et al. reported a case-control study that B-cell NHL is increased (adjusted odds ratio was 3.30) in HBV carriers.

HCC is well known malignancy in hepatitis B viral infected patient. Hepatitis B virus contributes to carcinogenesis according to several mechanisms. It can be integrated into the host genome and randomly inserted to adjacent of proto-oncogenes or tumor suppressor genes, which can activate proliferative signal pathways. In addition, active viral replication in the liver can cause inflammatory response and increase the risk of acceleration of mutations that contribute to neoplastic transformation. This process can be synergistically triggered by exposure to chemotherapeutic agent.

Generally, after administration of rituximab, HBV reactivation is not rare. Therefore, it is commonly well known that using prophylactic antiviral drug significantly decreased the incidence of HBV viral reactivation and disruption to chemotherapy, with a trend of improved clinical outcome such as overall survival.

In our study, the patient had chronic HBV infection with immune tolerated status and therefore started to receive antiviral agent prophylactically. However, the viral load did not decrease sufficiently after telbivudine treatment. Repeated rituximab treatment without sufficient viral clearance resulted in immune suppression and increased viral replication. Long-term immune dysfunction from underlying chronic hepatitis and repeated rituximab treatments were responsible for viral reactivation and emergence of resistance gene, finally it can lead HCC development.

In our opinion, before using B-cell depleting agent, it is necessary to use a potent antiviral agent than can sufficiently inhibit viral replication. During chemotherapy, the physician should check drug compliance and monitor liver function and mutation, regularly.

**REFERENCES**