Reactivation of Hepatitis B Infection During the Cause of Non Hodgkin's Lymphoma Chemotherapy

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ABSTRACT

Hepatitis due to hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy is a serious cause of liver-related morbidity and mortality. Frequently used combination regimens in Non-Hodgkin's lymphoma are cyclophosphamide, hydroxydaunomycin (adriamycin), vincristine (oncovin), and prednison (CHOP). The use of rituximab, a monoclonal antibody targeting CD20 antigen present in benign and malignant B-cells, in combination with systemic chemotherapy has resulted in an improved duration of remission and survival for this patients. Rituximab is a HBV reactivation risk factor even greater than corticosteroids in a series of patients with lymphoma treated with combined-modality treatment (CMT).

A 43 years old female patient who already diagnosed with Non-Hodgkin's lymphoma, came with chief complain nausea and vomiting for three weeks. The patient recently got hospitalized with icteric and known have positive HBsAg. She received chemotherapy rituximab CHOP (R-CHOP) for four times and got rituximab in the last chemotherapy. Previously she had icteric and increased liver function test. After exclude other possibility causes this symptom and sign, it was concluded this is HBV reactivation. The chemotherapy was postponed until this reactivation of hepatitis B resolved and start giving lamivudine two weeks before reintroduce chemotherapy.

Keywords: *antiviral treatment, chemotherapy, hepatitis B virus, reactivation*

ABSTRAK

Hepatitis dikarenakan reaktivasi virus hepatitis B (VHB) setelah pemberian terapi sitotoksik atau imunosupresi menyebabkan penyakit hati yang berhubungan dengan morbiditas dan mortalitas. Kombinasi regimen yang sering digunakan pada Non-Hodgkin's lymphoma adalah cyclophosphamide, hydroxydaunomycin (adriamycin), vincristine (oncovin), and prednison (CHOP). Penggunaan rituximab, sebuah antibodi monoklonal dengan target CD20 yang ada pada sel B yang tidak ganas maupun ganas, dikombinasi dengan kemoterapi sistemik akan memperbaiki waktu remisi dan angka hidup pada pasien tersebut. Rituximab merupakan faktor resiko reaktivasi VHB yang lebih besar dari pada kortikosteroid pada beberapa kasus pasien dengan limfoma yang mendapat terapi kemoterapi.

Dilaporkan pasien wanita usia 43 tahun yang telah terdiagnosa limfoma Non-Hodgkin datang dengan keluhan mual dan muntah selama tiga minggu dan telah menjalani rawat inap karena ikterik dan diketahui HBsAg positif. Pasien ini telah menjalani kemoterapi rituximab-CHOP (R-CHOP) sebanyak empat kali dan rituximab ditambahkan pada kemoterapi terakhir. Pasien ini sebelumnya mengalami kuning dan terdapat peningkatan pemeriksaan fungsi hati. Setelah menyingkirkan kemungkinan lain penyebab gejala dan tanda tersebut, disimpulkan bahwa terdapat adanya reaktivasi VHB. Dilakukan penundaan kemoterapi hingga terjadi perbaikan dari reaktivasi hepatitis B tersebut dan dimulai pemberian lamivudin selama dua minggu sebelum diberikan kembali kemoterapi.

Kata kunci: *terapi antivirus, kemoterapi, virus hepatitis B, reaktivasi*

INTRODUCTION

Reactivation of hepatitis B virus (HBV) which is stimulated by cytotoxic chemotherapy is a very important problem in patients with cancer. Increase in the amount of HBV usually preceeds "flare" hepatitis, and decompensated hepatitis and sometimes mortality is not rare when virus reactivation has started. HBV reactivation risk can be caused by patients' viral status and administered chemotherapy regiment. Chemotherapy regiment which consists of steroid and rituximab may increase risk virus reactivation in lymphoma patients. Therefore, HBV routine marker examinations are needed, including HBsAg and anti-HBc which are indispensable in all cancer patients, and antivirus prophylaxis therapy is strongly recommended in positive HBsAg cases.[1]

CASE ILLUSTRATION

A 43 year old women with stage IV Non-Hodgkin's lymphoma came to the outpatient clinic with complaints of nausea and yellow eyes since 4 weeks accompanied with brown colour urine. Previously, patient was hospitalized for three weeks due to nausea-vomiting and increased of absolute serum transaminase and serum bilirubin, including positive HBsAg were found. Patient was undergoing rituximab-cyclophosphamide-doxorubicin-vincristine-prednison (R-CHOP) chemotherapy and should undergo the fifth cycle of chemotherapy. She has no previous history of drug allergy. She got married once, had 3 children and worked as a housewife. She had no previous history of jaundice. Previous history of free sex and intravenous drug abuse were denied by both, the patient and her family.

From physical examination, it was found that blood pressure 110/70 mmHg, heart rate 80 bpm, and body temperature 36^{o}C. Other examinations resulted in anemic conjunctiva, icteric sclera and surgical scar in the abdomen area. Laboratory examination during her visit to the outpatient clinic revealed hemoglobin (Hb) 9.6 g/dL, trombocytes 86,000/µL, aspartate transaminase (AST) 102 U/L, alanin transaminase (ALT) 69 U/L, total bilirubin 13.21 mg/dL, direct bilirubin 11.76 mg/dL, albumin 2.21 g/dL. During the next visit, the followings were found: negative HBV DNA, negative HBeAg, and positive anti HBe. This showed that patient had reached "immune restoration" phase.

When patient underwent the first chemotherapy in June, it was found that the liver function was within normal limits. At that moment, initial examination for HBV was not performed. As she was undergoing fifth chemotherapy in September, she was hospitalized due to the complaints of nausea, vomiting, and lethargy. Laboratory examinations revealed absolute increase of liver transaminase (AST/ALT = 1,387/890 U/L), gradual increase of serum bilirubin (total bilirubin = 8.57 mg/dL), decrease of thrombocytes (56,000/µL), and positive HBsAg.

In this patient, chemotherapy was planned to be postponed for up to 100 days after the presence of HBV infection reactivation until free disease and immune restoration phase occurred. Patient would receive prophylaxis with lamivudine 100 mg per day for one week before undergoing chemotherapy again up to 6-12 months after chemotherapy was completed.

Pasien was followed-up for approximately three months without chemotherapy or antiviral drugs. In this patient, clinical and laboratory improvements were obtained. There had been seroconversion of HBeAg to negative HBeAg and the presence of anti-HBe. HBV DNA was not detected. HBsAg in the patient was still positive. Therefore, routine liver function and HBV DNA monitoring were still planned in this patient. Prophylaxis therapy would still be given in this patient, using lamivudine 100 mg/day for seven days before chemotherapy initiation up to 6-12 months after chemotherapy was completed.

DISCUSSION

HBV reactivation stimulated by immunosuppresive or cytotoxic chemotherapy drugs frequently occurs in HBV carrier and has wide range of symptoms, ranging from no symptoms to severe hepatitis with fatal complication. Reactivation does not occur only in positive HBsAg patients, but may also happen in negative HbsAg/positive anti-HBc, which is known as recovered hepatitis B case.[1]

Causes of HBV reactivation vary. Although reactivation may be spontaneous, most patients experienced virus infection reactivation due to "disturbance" which influences the balance between host immune and HBV activation. This may happen due to administration of immunosuppressants, cytotoxic chemotherapy, HIV infection or sudden cessation of antiviral therapy. Number of virus will increase in this condition. Later, rebound immune response and hepatitis reaction happened after cessation of the therapy. [1]

In patients who experienced reactivation, 53% experienced icteric hepatitis and 20% passed away. In a meta-analysis in 2008 which involved 14 studies in HbsAg carrier, the average reactivation

was approximately 33% (about 24-88%), with 33% hepatitis and 7% death from these cases. Therefore, reactivation does not occur in all positive HBsAg carrier who underwent chemotherapy. Some risk factors of reactivation were male, young age, early high HBV DNA replication (HBV-DNA > 20,000 IU/mL or positive HBeAg), administration of corticosteroid or rituximab chemotherapy regiment, and bone marrow transplant.[2] HBV reactivation does not usually happen until the second or third cycle of chemotherapy administration. It is unclear if this is caused by virus or host factor.[3] One of the studies stated that the highest degree of HBV reactivation was found in lymphoma cancer patients (58%), followed by breast (41%), head and neck (30%), lungs (23%), and digestive tract cancer (7%).[1]

Administration of rituximab has a higher risk factor of HBV reactivation as compared to corticosteroid. In several lymphoma patients who received chemotherapy, the only significant difference of HBV reactivation between recovered hepatitis group and without reactivation group is the use of therapy with rituximab alone or in combination with steroid. Rituximab is a monoclonal anti-lymphocyte B antibody which causes apoptosis, and B cell plays important role in various response towards HBV, in addition to neutralizer antibody, cell B plays role as antigen precenting cell and will increase CD8 cytotoxic lymphocyte response. Therefore, B cell impairment may decrease immune response to HBV replication. This also explains the reason rituximab may cause fulminant hepatitis and death in 50% patients with hepatitis who has recovered in seroconversion cases.[2]

The definition of HBV reactivation occurrence is suggested by Lok et al. The definition of HBV reactivation is the presence of sudden increase in the number of serum HBV (more than 10 times) or reappearance of HBV DNA in the serum. Additionally, hepatitis is defined as increase of serum ALT more than 3 times of normal value or absolute increase of ALT more than 100 U/L. To diagnose hepatitis due to HBV reactivation, clinician has to exclude the proof of liver infiltration of the underlying malignancy, hepatotoxic drugs, newly administered transfusion, and systemic infection for all cases.[4] HBV reactivation may be differentiated into 3 phases: increased virus replication, emergence of disease activity, and recovery.[5]

With routine serologic examination, it is currently known that liver impairment due to HBV reactivation passes through two phase process. Initially, during intensive cytotoxic or immunosuppressive therapy, there is increase of virus replication, described with the increase of serum HBV DNA, HBeAg, and HBV DNA polymerase due to infection expansion in the hepatocyte. Along with the recovery of immune function due to cessation of cytotoxic or immunosuppresive therapy, there will be rapid destruction mediated by immune to HBV infected hepatocyte, which clinically manifest as hepatitis, liver failure, or even death.[3]

Nausea and vomiting are side effects of various drugs which usually occur at initial administration. Many factors play role in the appearance of severe symptoms in chemotherapy-induced nausea. Each drug has specific emitogenic potency (from mild, moderate, to severe). Depending on the chemotherapy agent, emitogenic potency may increase as the dose is increased. Cyclophosphamide emitogenic potency may be moderate to severe depending on the dose. When chemotherapy agents are given simultaneously with drugs, such as: cyclophosphamide and doxorubicin, the emitogenic potency is higher compared to those agents administered alone. Chemotherapy-induced vomiting is usually more common to occur in female and young aged patients.[6] In this patient, severe nausea-vomiting accompanied with increased liver transaminase and serum bilirubin were found. This showed the presence of liver impairment which underlied patient's complaint of nausea-vomiting, not only just due to chemotherapy agents.

Liver impairment during chemotherapy may not always describe hepatotoxicity from anti-cancer agents. Although many agents may cause liver impairment, most hepatotoxic reaction from drugs are idiosyncratic, due to immunologic reaction or variation of body metabolic response. This reaction particularly does not depend on the drug dose.[7] Liver impairment mediated by immune may cause fever, skin redness, eosinophilia, and presence of antibody.[8] In this patient, there was no complaint of redness on skin, eosinophilia, or even positive autoantibody. Therefore, the initial diagnosis of serum transaminase due to chemotherapy agents could be kept aside.

Autoimmune hepatitis (AIH) is a disease with unknown etiology, with specific characteristic of presence of defect in suppressor T-cell with autoantibody which directly attack hepatocyte surface antigen. AIH predominantly attacks young and middle aged female. The presenting symptoms include fever, lethargy, skin redness, polyarthritis, pleuritis, pulmonary infiltration, or glomerulonephritis. In examination, there was increased liver transaminase, hypergammaglobulinemia, and positive autoantibody

(antinuclear antibody (ANA), smooth muscle antibody (SMA), or liver kidney microsomal type 1 (LKM1).[9] In this patient, there was no fever, skin redness, polyarthritis, pleuritis, or even glomerulonephritis. Autoantibody in this patient was negative. Therefore, the initial diagnosis of increased serum transaminase due to autoimmune hepatitis could be excluded.

HBV infection reactivation in asymptomatic hepatitis carrier patient who is undergoing chemotherapy has potency to have fatal complication. In previously healthy patient who suffered from acute hepatitis, recovery may happen in almost 99% patients, therefore antiviral therapy is not needed. In severe acute hepatitis which rarely happen, therapy using oral dose nucleoside analog, which is usually used for chronic hepatitis B therapy, may be performed with high success rate. Although through clinical research this has not been proven effective, acute and severe hepatitis B infection are still not indicated to be treated.[10]

In cases where HBV reactivation occur during chemotherapy, delaying cytotoxic therapy may be required up to 100 days, will give free disease phase and ability to survive generally in patients with malignancy who is associated with HBV reactivation. Mortality rate which is directly associated with HBV reactivation, secondary predominant to acute liver failure, varies from 4% up to 60%. In patients who experienced reactivation during or associated with delaying chemotherapy, immunosuppressant, or other cytotoxic therapy, treatment choice is more difficult and less effective. This is because of the treatment effect in inhibiting immune response which underlies liver impairment, thus treatment is usually ineffective.[11,12]

Based on the data and protocol from various studies, it is recommended that all HBsAg carrier receive prophylaxis lamivudine 100 mg/day starting 7 days before chemotherapy initiation.[10,11] The duration of optimal lamivudine administration is still unclear, however it can be given 6-12 months after chemotherapy is completed to prevent delayed HBV reactivation.[1,2,11]

Lamivudine is a nucleoside analog which is firstly approved to be used in the treatment of chronic hepatitis B. Prophylaxis effect of lamivudine in HBV reactivation in carrier hepatitis B during chemotherapy has been proven in two randomized studies (RCT). Incidence of HBV reactivation in lymphoma patients with positive HBsAg who received lamivudine prophylaxis was 0% and 31% compared to 53% up to 65% in controls. Incidence of severe acute hepatitis and mortality also decreased with lamivudine prophylaxis. HBV infection reactivation may also happen after completing chemotherapy and cessation of lamivudine prophylaxis, so it is known as delayed HBV reactivation, which rarely happens. Administration of preventive antiviral with adequate duration is very important in giving protective effect. Besides lamivudine, entecavir, telbivudine, and tenovovir are currently available for treatment of chronic hepatitis B and chemopreventive. Although the use of those prophylaxis antivirals are still limited.[1]

Based on 3 guidelines of HBV therapy from the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL), and Asia-Pasific Association for the Study of Liver (APASL), HBV markers, including HBsAg and anti-HBc need to be evaluated in all cancer patients before chemotherapy is performed. To prevent HBV reactivation risk in carrier patient which can be life-threatening, antiviral therapy as routine prophylaxis is recommended in positive HBsAg patients before cancer chemotherapy is started. Duration of antiviral prophylaxis administration need to be prolonged for at least 6 months after therapy completion to prevent delayed HBV reactivation. Ideally antiviral prophylaxis therapy administration is continued until the end-point is achieved (seroconversion of HbeAg in positive HBeAg; the persistence of suppression of HBV DNA until not detected and disapperance of HBsAg in negative HBeAg patients), and this is recommended by AASLD to patients with initial high viral load (> 2000 IU/ml). Antiviral drug with low genetic barrier, such as: lamivudine or telbivudine may be used if the length of therapy is less than 12 months, or when HBV amount is low in initial examination: or high genetic barrier medicine, such as entecavir or tenofovir can be used.[1]

There is still no recommendation made for the use of antiviral prophylaxis before chemotherapy in positive anti-HBc but negative HBsAg patients. However, HBV DNA need to be examined in positive anti-HBc patients without considering the anti-HBs status. Continuing HBV DNA examination need to be performed to detect the presence of HBV reactivation, and antiviral therapy need to be given as soon as possible if HBV DNA has increased 10 times from the baseline, and > 2000 IU/ml during chemotherapy administration.[1]

In this patient, initial serologic examination towards hepatitis B before chemotherapy administration was not performed. After undergoing the fourth cycle of chemotherapy, there was complaints which are associated with the presence of acute hepatitis, increased absolute serum transaminase, hyperbilirubinemia, hypoalbuminemia, and thrombocytopenia. In that

fourth cycle, patient was given additional rituximab. During examination, she had positive HBsAg. After 2 months, hepatitis B markers were evaluated; there was negative HBV DNA and negative HBeAg, which showed that there had been seroconversion without antiviral drug administration. After passing the acute hepatitis phase, we gave the patient antiviral prophylaxis with lamivudine 100 mg per day before the reinitiation of RCHOP chemotherapy for Non-Hodgkin lymphoma. Patient would be followed-up and routine examination of HBV DNA would be conducted until chemotherapy completion to see if there would still be HBV reactivation in this patient.

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