Role of Lamivudine as Preemptive Therapy in Cancer Patients with Hepatitis B undergoing Chemotherapy

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ABSTRACT

Patients diagnosed with hematology malignancy and solid tumor who underwent chemotherapy, frequently encountered hepatitis B reactivation. Patients with blood cancer, including lymphoma, had higher risk of reactivation compared to those with solid tumor. Steroid and immunosuppressant drugs contained in chemotherapy regimens were responsible for those events. Hepatitis B reactivation during chemotherapy treatment could contribute to acute liver failure and increase mortality. Administration of analog nucleoside therapy in this group of patient prior to the initiation of chemotherapy could prevent reactivation of hepatitis B.

A 43 year-old male patient were diagnosed with diffuse large B cell non-Hodgkin lymphoma stadium II BE (oropharynx) under chemotherapy and had hepatitis B. In this evidence based case report, we reported a critical appraisal of the role of lamivudine as preemptive therapy in blood cancer and solid tumor.

Keywords: *chemotherapy, hepatitis B reactivation, malignancy*

ABSTRAK

Pasien dengan diagnosis dengan keganasan darah dan tumor padat yang menjalani kemoterapi, seringkali mengalami reaktivasi dari hepatitis B. Pasien dengan keganasan darah termasuk limfoma, memiliki risiko reaktivasi yang lebih tinggi dibandingkan pasien dengan tumor padat. Steroid dan obat imunosupresan yang merupakan bagian dari regimen kemoterapi dapat menyebabkan terjadinya hal tersebut. Reaktivasi hepatitis B pada saat menjalani regimen kemoterapi dapat menyebabkan gagal hati akut yang meningkatkan angka mortalitas. Pemberian nukleosida analog pada kelompok pasien tersebut dapat mencegah terjadinya reaktivasi hepatitis B.

Seorang pasien laki-laki usia 43 tahun didiagnosis dengan penyebaran sel besar B non Hodgkin limfoma stadium II BE (orofaring) dibawah kemoterapi dan memiliki hepatitis B. Pada laporan kasus berbasis bukti ini dilaporkan hasil telaah kritis peran lamivudine sebagai terapi pre-emtif pada keganasan darah dan tumor padat.

Kata kunci: *kemoterapi, reaktivasi hepatitis B, keganasan*

INTRODUCTION

More than 350 million people in the world were infected by hepatitis B virus (HBV). Chronic HBV infection is a main health problem and is the most common cause of liver cancer in Asia and Africa. In the United States, HBV infection prevalence which is defined as the presence of HbsAg in the blood, is found less than 1% in population but it is 5-15% among immigrants from Asia, Africa, Middle East, and Eastern Europe.[1] HBV infection may cause chronic liver disease, cirrhosis, and liver cancer. While many patients had HBV in their serum and hepatocytes

for years, only a few showed clinical effects. These individuals are considered in hepatitis B surface antigen (HBsAg) carrier state and few evidence showed presence of liver disease despite the low replication rate of HBV in the liver cells. In such individuals, immunosuppresive agents may trigger enhancement of HBV replication followed by hepatitis B flaring which can be severe and fatal.[1]

Reactivation of HBV infection has been observed in several clinical settings such as in liver transplantation, partial liver resection in hepatocellular carcinoma, pregnancy, and immunosuppresion (either due to iatrogenic or infective cause, including chemotherapy and HIV infection), immunosuppression withdrawal, bone marrow transplantation or even spontaneously.[1,2] The immunosuppresive nature of chemotherapy could cause HBV flares in people who has HbsAg in their sera. Reactivation may occur despite the normal level of ALT and low titer of circulating virus prior to the initiation of chemotherapy and eventually would increase morbidity and mortality.[1,2]

In a prospective study, it was obtained that more than 60% of HBV reactivation took place in HbsAg-positive patients receiving cytotoxic therapies. Cytotoxic therapy, with or without adjuvant immunomodulator therapy, would affect the risk of reactivation. Patients with blood cancer, including lymphoma, receiving high dose glucocorticoid as part of their chemotherapy regiments were considered to have a higher risk of reactivation (up to 67%) compared to those who were associated with solid tumors (< 40%).[2] In cases of HBV reactivation during the early phase of chemotherapy, cytotoxic therapy should be delayed for 100 days, due to the survival rate of patients with malignancy complicated by HBV reactivation. Mortality rate directly associated with HBV reactivation, which leads to acute liver disease, varies from 4-60%.[2]

CASE ILLUSTRATION

A 43 year-old male patient were diagnosed with diffuse large B cell Non Hodgkin Lymphoma stadium II BE (oropharynx) under chemotherapy and had hepatitis B. He was scheduled to undergo chemotherapy the following week. A few years ago, he routinely donated his blood to Indonesian Red Cross and was found to be HbsAg positive. Other examinations to diagnose hepatitis B have never been performed. There was no history of multiple partners. He also denied any history of nausea, vomiting, upper abdominal pain, or jaundice. He never had any episode of vomitting of blood, black "tarry" stool, abdominal distension, and leg swelling. History of past illness did not reveal any history of hypertension, diabetes, cardiovascular disease, asthma, allergy, and jaundice. There was also no history of similar disease in his family.

On physical examination, his vital signs were within normal limits. There were no pale conjunctiva nor icteric sclera. The patient had tracheostomy tube. Heart and lung examinations were normal. Abdominal examination showed flat abdomen, no abdominal tenderness, no liver or spleen enlargement, no shifting dullness and normal bowel sound. There was no stigmata of cirrhosis such as hair loss, spider nevi, caput medusa, venectation, leg swelling, palmar erythema, or flapping tremor. Laboratory examination revealed normocytic normochromic anemia (hemoglobin 8.9 g/dL); slightly increased transaminase enzymes (aspartate aminotransaminase (AST) 40 U/L and alanin transaminase (ALT) 64 U/L); serum iron 17 µg/dL; total iron binding capacity (TIBC) 269 mcg/dL; ferritin 729.4 µg/L, HbsAg titer 4,373.0 IU/mL considered as reactive and anti hepatitis C virus (HCV) 0.08 considered as non-reactive. Other peripheral blood examination, serum electrolytes, kidney function test and blood glucose were within normal limits. He was then diagnosed with diffuse large B cell non Hodgkin malignant lymphoma stadium II B type with oropharyngeal extranodal involvement with a plan of chemotherapy using rituximab, cytoxan, hydroxydaunorubicin, oncovin, prednisone (R-CHOP) on the third cycle complicated by anemia of chronic disease and hepatitis B. To the patient, lamivudin 100 mg was planned to be given daily started from 1 week prior to chemotherapy until 3-6 months thereafter.

Clinical Problem

Based on the findings of some studies, lamivudin therapy for HbsAg carrier receiving immunosuppresive agents or other chemotherapy has shifted from therapy after the reactivation had been diagnosed to prophylaxis therapy prior to chemotherapy. This has become the basis for further evaluation on effectivity and safety of lamivudine as preemptive therapy in HbsAg carrier, especially in patients with blood cancer and solid tumor undergoing chemotherapy.

On that basis, clinical questions arised: "what is the role of lamivudine as preemptive therapy in patients with blood cancer and solid tumors complicated by hepatitis B who undergo chemotherapy?" and "will preventive therapy using lamivudin decrease the risk of HBV reactivation, hepatitis associated with

HBV, liver failure due to HBV or HBV-associated death, in patients with positive HbsAg who undergo chemotherapy?"

Tracking Method and Result

Literature searching method used to answer the clinical question was online literature searching using Pubmed search engine. The keywords used were "*lamivudine AND preemptive therapy AND chemotherapy"*, limited by: study on human and publication in English.

Using this method, 28 articles which fulfilled the criteria were collected. Further searching using relevant references were done manually. At the end of the literature searching, some relevant articles, consisted of clinical trials, were obtained to answer these clinical questions. Level of evidence were defined based on the classification published by Oxford Centre for Evidence-based Medicine Level of Evidence.

Ziakas et al performed a meta-analysis on 95 related publications. After the evaluation of relevant and conclusive publication data completeness, 9 studies that met the criteria were obtained. These studies involved 396 people; 127 patients on the prophylactic lamivudine arm and 269 patients on the control group. Cummulative prevalence of HBV reactivation on the prophylactic group was 8.6% (11/127) vs. 50.6% (136/269) on the control group. Reactivation incidence on patients who did not receive prophylaxis varied from 54.5-100% while the incidence of reactivation in the prophylactic study group was not more than 5%.[3]

The largest randomised, prospective study regarding lamivudine prophylaxis in non Hodgkin lymphoma patients undergoing chemotheraphy showed that lamivudine prophylaxis, after multivariate analysis, was the only independent factor which could predict HBV reactivation (OR = 0.04; 95% CI = 0.005-0.344). Although HBV reactivation occurred during chemotherapy, incidence and severity of hepatitis flare reduced significantly.[3]

Lamivudine prophylactic effects accumulatively remained significant on forrest plot in a fixed effect model (RR = 0.21; 95% CI = 0.13-0.35) without evidence of heterogeneity between studies while clinical heterogeneity existed. As for the mortality rate, combined effect of 8 studies reported insignificant decrease clinically by 15/254 (5.9%) in control group and 2/117 (1,7%) in prophylaxis group (RR = 0.68; 95% CI = 0.19–2.49).[3] The conclusion of this meta-analysis was prophylaxis using lamivudine was associated with significant reduction of HBV reactivation (RR = 0.21; 95% CI = 0.13-0.35) and the trend of HBV-associated death (RR = 0.68; 95% CI = 0.19-2.49). Besides, prolonged time of anti-HBV prophylaxis may increase survival rate up to 2.4% in HBsAg-positive patients.[3]

A systematic review conducted by Kohrt et al on 9 prospective studies and one randomized controlled trial (RCT) revealed that the rate of hepatitis among subjects receiving lamivudine prophylaxis was between 0-20% compared to that of the control group, 33-67%. Among patients who received prophylaxis, 0-24% of them had HBV reactivation compared to 29-56% in the control group. Three reactivation cases were related to mortality (one subject received prophylaxis, the other two were controls). No patients were excluded from the study due to toxicity or emerging mutation resistant against lamivudine.[2]

Lau collected literature from 2002-2006 about lamivudine as preemptive therapy and obtained 13 reports. Meta-analysis of these 13 studies of 702 HbsAg-positive patients (237 were treated with preemptive lamivudine and 465 were controls who did not receive lamivudine) showed that incidence of hepatitis due to HBV reactivation were 3.3% in the treated group and 35% in the control group with OR = 0.083; 95% CI = 0.045-0.155; $p < 0.0001$.[4-13] Therefore, there was a strong believe considering beneficial effects of preemptive lamivudine to reduce hepatitis due to HBV reactivation in HbsAg patients receiving cytotoxic or immunosuppressive therapy. However, most of these studies were retrospective ones without any control groups who did not receive therapy.[4-13]

Loomba et al performed a systematic review of several clinical trials and cohort studies reporting the efficacy of prevention against HBV reactivation using lamivuding in HbsAg-positive patients who received chemotherapy. Additional criteria included minimum sample size (> 5 participants in each treatment group) and reported data on HBV-related morbidity and mortality.[14] Fourteen studies (two clinical trials with control group and randomization; eight prospective cohort studies; and four retrospective cohort studies) meta analysis criteria. There were 275 patients in the group treated with lamivudine and 475 patients in the control group with HBV reactivation as primary end point. Using lamivudine, the relative risk of HBV reactivation and HBV-associated hepatitis varied between 0.00-0.21. There was no patient in the lamivudine group developed liver failure associated with HBV (0 out of 108 vs. 21 out of 162 patients)

and only 4 deaths were caused by HBV (4 out of 208 patients vs. 27 out of 394 patients) in the lamivudine group. Lamivudine was well torelated and no side effects was found.[14] The conclusion of this systematic review was that lamivudine treatment in patients with HbsAg positive and will undergo chemotherapy might reduce the risk of HBV reactivation and HBV-related morbidity and mortality.[14]

Hui et al evaluated the proposed duration of preemptive therapy using lamivudine. In a study of 46 patients with HbsAg positive who received preemptive lamivudine, the therapy was started 1 week prior to chemotherapy and was continued during chemotherapy. Preemptive lamivudine was stopped with a median of 3.1 months (range 3-3.4) after chemotherapy. These patients were then observed after cessation of lamivudine with median duration of follow up 25.7 months (range 5.7-75.7).[15]

Eleven patients out of 46 (23.9%) developed HBV reactivation after lamivudine was stopped. Eight out of 16 patients with high copies of HBV DNA prior to chemotherapy (> 104 copies/mL) had HBV reactivation (50% vs. 10%; p = 0.001). HbeAg-positive patients were more probable to have HBV reactivation (5/11 (45%) vs. 6/35 (17.1%); p = 0.041). Patients with high copies of HBV DNA prior to chemotherapy were the most important risk factor to develop HBV reactivation after the cessation of lamivudine preemptive therapy on proportional hazards Cox analysis (RR = 16.13; 95% CI = 99-87; p = 0.001).[15]

Kim et al conducted a study to foresee the long term effects of lamivudine therapy in prevention of HBV reactivation and HbeAg-related morbidity. Twenty four patients with non Hodgkin malignant lymphoma were given lamivudine 100 mg daily prior to initiation of chemotherapy. Treatment duration was approximately 11.5 months, ranging from 1-54 months, and the median of chemotherapy cycles was 6 (range 1-16 cycles). Chemotherapy regimens using steroid were used in 18 (75%) patients and anti CD-20 monoclonal antibody was used in 6 (25%) patients.[16]

The result was that hepatitis associated with HBV reactivation emerged in 1 out of 14 patients with positive HbeAg and none occurred in 10 patients with negative HbeAg. One patient developed HBV reactivation after lamivudine cessation and 4 patients had YMDD mutation (tyrosine-methionine-aspartate-aspartate) during lamivudine treatment. There was no statistically significant difference of HBV reactivation during chemotherapy based on HbeAg status. It was concluded that lamivudine should be considered as preemptive treatment prior to chemotherapy in every patients with non Hodgkin malignant lymphoma to prevent HBV reactivation regardless of HbeAg status before chemotherapy.[16]

DISCUSSION

Cancer is the cause of death in the United States, where most people undergo chemotherapy throughout their lives. Therefore, though the prevalence of HbsAg carrier is low, prevention of HBV reactivation due to chemotherapy becomes an important medical problem and attention in health sector. This problem becomes more important in some parts of the world where HBV infection was endemic.[2,14]

Lamivudine is nucleoside analog which effectively suppresses HBV replication and decreases the level of HBV DNA in the serum and improve liver injury in patients with chronic hepatitis B. Lamivudine also has good long term safety profile and in general can be well tolerated. Several studies reported the benefit in preventing HBV reactivation and death caused by HBV in HbsAg positive patients and will undergo chemotherapy.[14]

Initial report of lamivudine revealed that it might cause suppression in HBV replication due to early termination of DNA chain, which seemed to be promising for chronic hepatitis B therapy. In in vitro studies, lamivudine has relatively lower profile of side effects without significant hematopoetic toxicity in HBV reactivation after chemotherapy or immunosuppression.[2]

First clinical trial reported suppression and decrease of HBV DNA serum in chronic hepatitis B patients and also acute. Previously, series of cases have shown the efficacy of lamivudine in treating HIV infected patients who had been coinfected with hepatitis B. Other series of case reports also showed the evidence that in vivo lamivudine is effective in the treatment of HBV infected patients who are immunosuppressed and safe for patients with chemotherapy associated cytopenia. Role of lamivudine in the treatment of HBV reactivated was further reported on 2 studies, which were reactivation of hepatitis fulminant case after chemotherapy in lymphoma and acute jaundice hepatitis in allogenic bone marrow transplant patients who receive immunosuppression.[2]

Although lamivudine response were seen in most patients, 18-40% patients did not improve by lamivudine therapy. Profile between patients who failed to respon to lamivudine were because they

started lamivudine therapy late. Based on these findings, therapy for chronic HbsAg carrier who receive immunosuppressive agents or chemotherapy has shifted from therapy after reactivation is diagnosed to prophylaxis before initiation of chemotherapy.[2,14]

Early case report on primayr prophylaxis was included 20 patients with blood malignancy and variety chemotherapy regimens, most of which included glucocorticoid. With 5% reactivity rate of HBV, lamivudine role in prophylaxis among HbsAg carrier had been indicated. However, following study stressed on the possibility of lamivudine-resistent mutant and increased mortality among some patients which was treated with lamivudine.[2]

In the result of first search study, a meta-analysis conducted by Ziakas et al obtained 9 relevant studies and with the meta-analysis result as depicted, it was obtained the result that supported previous studies; that all patients diagnosed with lymphoma should undergo HBV screening. All HbsAg carriers should have received preemptive antiviral therapy during maintanance phase of chemotherapy. Strategies to prolong prophylaxis will increase survival rate through decreased reactivation of HBV and HBV associated mortality.[3]

Meanwhile, results of second search from a systematic analysis performed by Kohrt et al concluded that decreased up to four to seven fold in terms of hepatitis and hepatitis B virus reactivation in patients receiving lamivudine. Thus, it is recommended that all HbsAg carrier patients received lamivudine or antiviral which was equal as prophylaxis before chemotherapy initiation until, at least, one year after chemotherapy is completed. [2]

Based on a level 3 evidence, in year 2004 American Association for the Study of Liver Disease (AASLD) recommended continuation of prophylactic lamivudine up to 6 months after chemotherapy is completed and is prolonged in 2007 update for patients with high basis of HBV DNA (defined by serum HBV DNA > 2,104 copies/mL). Then, in year 2009 AASLD recommended that antiviral prophylactic therapy should be given in hepatitis B carrier (regardless the previous HBV DNA level) during initiation of chemotherapy or immunosuppressive therapy with limited time and was maintained for 6 months after it.[17]

Viral relapse after discontinuation of lamivudine has been reported in patients with high level of HBV DNA before chemotherapy, HbsAg positive with HBV DNA serum level > 2,000 IU/mL before initiation of chemotherapy should have continued the antiviral therapy until treatment target as for chronic hepatitis B patients is reached. In patients whose level of HBV DNA < 2,000 IU/mL, they should have continued therapy until 6 months after discontinuation of chemotherapy or immunosuppression. Lamivudine or telbivudine can be used if the duration of therapy is short (< 12 months) and level of serum HBV DNA is not detected. Tenofovir or entecavir is more preferred if the duration of therapy is longer. Interferon should be avoided due to its suppression effect to the bone marrow.[17]

A recommendation issued by Canadian Society stated that each patients who will undergo chemotherapy or bone marrow transplantation should be tested for HBV marker prior to the treatment. For those who are HbsAg-positive, preemptive lamivudine therapy should be applied to prevent hepatitis flares which may take place during the treatment. Since hepatitis flares occured as the result of immune recovery, lamivudine therapy should be initiated several days prior to induction of immunosuppressive therapy.[18]

Meanwhile, European Association for the Study of the Liver (EASL) recommendation of preemptive therapy before immunosuppression or chemotherapy is for all HBV carrier patients who received chemotherapy or immunosuppression due to high reactivation risk, particularly if rituximab is given alone or combined with steroid. HBV vaccination in seronegative patients is highly recommended. EASL also recommends to examine HBV DNA level before chemotherapy initiation and receive preemptive therapy during therapy (regardless of HBV DNA level) and for 12 months after cessation of chemotherapy.[19] EASL recommendation for negative HbsAg patients with positive anti-HBC and undetected serum HBV DNA who will receive chemotherapy and or immunosuppression should be followed-up for ALT and HBV DNA examination and treated during positive HBV reactivation before elevation of ALT.[19]

The Asian Pasific Association for the Study of the Liver (APASL) recommendation states that lamivudine is effective in preemptive therapy in cancer patients who will undergo chemotherapy starting in 1 week before chemotherapy is started and continued to at least 12 weeks after chemotherapy was completed and after leucocyte count is back to normal.[20]

Consensus of Indonesian Association for the Study of the Liver for chronic hepatitic B infection in 2006 also recommended lamivudine therapy before administration of immunosuppresive agent or chemotherapy which is then continued up to at least 6 weeks after treatment is proven to be effective in preventing reactivation.[21]

Patients with blood malignancy and solid tumors who will undergo chemotherapy should have been examined for their HBV status, which is HbsAg status for initial examination. If positive HbsAg was obtained and patient will undergo chemotherapy, administration of lamivudine as preemptive therapy has been proven in many studies for its effectivity in decreasing HBV reactivation risk, HBV associated hepatitis, liver failure or even survival. Regarding administration time, several studies agree to be administered a week before chemotherapy was started. In terms of duration of lamivudine prophylaxis administration, some studies vary and even recommendation for America, Europe or Asia Pacific are between 3-12 months after chemotherapy is completed.

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