Comparison between Entecavir and Lamivudine as Hepatitis B Reactivation Prophylaxis in Cancer Patient with Chemotherapy

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ABSTRACT

Aim: *To compare between entecavir and lamivudine as hepatitis B reactivation prophylaxis in cancer patient with chemotherapy*

Method: *A literature searching in PubMed was done. At the beginning, 8 articles were found. Chosen article in this EBCR were those which compared lamivudine and entecavir directly to lymphoma patient in chemotherapy. Six articles were excluded. Besides PubMed, literature searching was done in Highwire, Cochrane, and Google Scholar too. In Google Scholar, one article that compared entecavir and lamivudine as hepatitis B prophylaxis in cancer patient was found in this study, there were also two multicenter retrospective study that will be appraised.*

Results: *Hepatitis B virus (HBV) reactivation, HBV related hepatitis, and chemotherapy discontinuity as a consequence of Hepatitis B were found to be lower in entecavir groups. Entecavir was more effective in subjects with measured HBV deoxyribonucleic acid (DNA). In unmeasured HBV DNA groups, entecavir were as effective as lamivudine.*

Conclusion: *Entecavir were found to be more effective than lamivudine in patient with positive HBsAg or advanced stage of malignancy that were prepared for aggressive chemotherapy regiments. Since entecavir cost was unaffordable, lamivudine still a drug of choice in this situation.*

Keywords: *entecavir, lamivudine, prophylaxis hepatitis B reactivation, chemotherapy*

ABSTRAK

Tujuan: *Mengetahui mengenai perbandingan entecavir dan lamivudine sebagai profilaksis reaktivasi hepatitis B pada pasien keganasan dalam kemoterapi.*

Metode: *Dilakukan pencarian literatur di PubMed. Dari pencarian awal di Pubmed, diperoleh 8 artikel. Artikel yang terpilih dalam EBCR ini adalah studi yang membandingkan lamivudine dan entecavir secara langsung pada pasien limfoma dalam kemoterapi. Sejumlah 6 artikel dieksklusi. Selain Pubmed dilakukan juga pencarian artikel di Highwire, Cochrane dan Google Scholar. Pada Google Scholar ditemukan satu artikel yang membandingkan entecavir dan lamivudine sebagai profilaksis hepatitis B pada pasien keganasan. Pada laporan ini, terdapat dua studi multisenter retrospektif yang akan dilakukan telaah lebih lanjut.*

Hasil: *Angka reaktivasi hepatitis B virus (HBV), hepatitis terkait HBV dan terputusnya kemoterapi akibat hepatitis lebih rendah pada kelompok entecavir. Entecavir lebih efektif pada kelompok subjek dengan kadar HBV deoxyribonucleic acid (DNA) terukur. Pada kelompok subjek dengan HBV DNA tidak terukur entecavir memiliki efektivitas yang sama dengan lamivudine.*

Simpulan: *Entecavir lebih efektif dibandingkan lamivudine pada pasien dengan status HBsAg positif ataupun pasien yang memiliki keganasan stadium lanjut dan akan menjalani kemoterapi jangka panjang dengan regimen yang berat. Akan tetapi karena biaya entecavir yang masih belum terjangkau maka lamivudine masih merupakan terapi pilihan pada kasus ini.*

Kata kunci: *entecavir, lamivudine, profilaksis reaktivasi hepatitis B, kemoterapi*

INTRODUCTION

Hepatitis B infection were one of the risk factors of hepatocellular carcinoma (HCC) and reported to infect more than 350 million people worldwide. Besides interferon therapy, analog nucleoside therapy such as lamivudine, adefovir, and entecavir were a new promising antiviral to inhibit reverse transcriptase enzyme of HBV.[1] HBV reactivation could also occur during the use of chemotherapy agents or immunosuppressive agents.[1] It has been reported that HBV reactivation were found higher in lymphoma malignum, hematologic malignancy, and other rheumatologic and oncologic disease.[2] HBV reactivation risk were proportional to immunosuppressive therapy alongside whatever patients hepatitis B surface antigen (HBsAg) status.[1] Various report showed that HBC reactivation were commonly occur in lymphoma malignum on combination chemotherapy such as rituximab and steroid, with incidence rate 14-72%.[1,3] Koo et al investigated that patients with advanced stage disease have a higher risk of HBV reactivation.[4] In those patients, HBV reactivation could lead to fulminant hepatitis or even liver failure. Because of that, the need of hepatitis B reactivation during chemotherapy period with immunosuppressant should be further discussed.[2]

Lamivudine was a nucleoside analog to inhibit ribonucleic acid-dependent (RNA-dependent) deoxyribose nucleic acid (DNA) polymerase in HBV replication cycle, reduce HBV DNA in serum, and repair liver tissue damage in HBV infection. Lamivudine was well tolerated and safe for chronic use. Otherwise, recently a long period use of lamivudine were associated with drug-resistant tyrosine-methionine-aspartate-aspartate mutation risk.[5]

Entecavir was a nucleoside analog considered potentially better antiviral effect than lamivudine with lower resistances in prevent HBV reactivation.[6] Several studies about how chronic use of lamivudine could evoke its resistance lead to a question about how effective entecavir as a drug of choice in Indonesia for HBV reactivation prophylaxis in chemotherapy patients. This is the reason why this topic were discussed in this evidence-based case report.

CLINICAL QUESTION

A 45 years old male patient, unemployed, married and have 3 child with Gakin health insurance came to Hematology Clinic in RSCM recommended to 3rd cycle of RICE (rituximab, ifosfamide-carboplatin-etoposide) chemotherapy. One year before he came to hospital, patient was complaining about a lump in his left neck and two other lump in his axilla as big as marbles, firm, and immobile. Patient then done a biopsy procedure, told to have lymph node malignancy. Six months before came into hospital, patient were also undergo ultrasonography (USG) procedure, told to have a swollen kidney and recommended to implant a DJ stent. Patient was also complaining about abdominal bloating, and dyspnea during supine position. Fluid were found in patient lung and drained during one month hospitalization. Patient then underwent a cyclophosphamide-hydroxydaunirubicine-oncovin-prednisone (CHOP) chemotherapy once (5 months before hospitalization) with abdominal bloating and reduce dyspnea. There was improvement in apetite. Patient then continues a three section of chemotherapy using CHOP. After the evaluation, disease were considered as stable so that chemotherapy could be switched into rituximab-ifosfamide-carboplatin-etoposide (RICE). At present, febrile, night sweat, dyspnea, and abdominal bloating were denied by patient. Patient were diagnosed hepatitis B from six month before hospitalization and given lamivudine therapy of 1x100 mg. Patient denied any hepatitis history, and also denied diabetes mellitus, hypertension, asthma, allergy, and cardiovascular disease history. Patient's child were having a nasopharyngeal

carcinoma. A tattoo were found in patients arm with alcoholism history, but denied promiscuity, abuse needle use, and any transfusion history.

During physical examination, patient was compos mentis, looks ill, with vital sign considered normal. There were no abnormality in eye, neck, lung, and heart examination. There were no hepatomegaly and splenomegaly. There were no neck, axilla, supraclavicular, and inguinal lymph node enlargement. Hematologic examination shows an normocytic normochromic anemia with Hb 10.2 g/dL, and normal transaminase (AST/ALT 23/16). Hepatitis marker laboratory examination shown a positive in HbsAg, anti-HBe, and total anti-HBc. Pathologic findings showed diffused lymphoma malignum with large cell type and moderate malignancy grade. Immunohistochemistry examination showed a positive in CD 20, CD 3, CD 5, KI-67, and bcl-2 with conclusion as lymphoma malignum non-Hodgkin, B cell, large, and diffuse from the pathologist. Bone marrow biopsy showed a hypercellular without metastasis. Thorax plain photograph showed an pleural effusion of left lung, but diminished in the next month. Echocardiography examination considered normal. Abdominal USG showed a liver cirrhosis with malignant tendency, bilateral pleural effusion, paraaortic lymph node enlargement, and bilateral hydronephrosis. CT scan examination revealed an paraaortic lymph node enlargement from hepatic hylum into abdominal aorta bifurcation with prominent bilateral hydronephrosis. After two chemotherapy, CT scan examination showed reduce of paraaortic lymph node size and hydronephorsis was disappeared, but pleural effusion and a lesion in vertebral column Th12-L4 were founded. Pleural fluid examination showed an non-Hodgkin lymphoma malignum cell. At present, patient were prepared for the third RICE, ranitidine 2x50 mg, ondansetron 3x8 mg, curcuma 3x200 mg, and lamivudine 1x100 mg. After the third chemotherapy, transaminase were increase more than three times AST/ALT 209/197 u/L with bilirubin total/direct/indirect account 3.82/2.61/1.22 mg/dL respectively.

From the illustration above, the clinical question for this situation defined as what is the best HBV reactivation prophylaxis therapy for patient with malignany in chemotherapy: lamivudine or entecavir?

METHOD

To find an answer of the clinical question above, we formulate a PICO table to guide the literature searching (Table 1)

Table 1. Formulation of PICO question

Variable	Identification
Problem	HBV reactivation in lymphoma ongoing a chemotherapy
Intervention	Entecavir
Comparison	Lamivudine
Outcome	No HBV reactivation

A literature searching in PubMed was done with keywords: entecavir AND lamivudine AND lymphoma chemotherapy. In details: (“ lamivudine”[MeSH Terms] OR “lamivudine”[All Fields] AND (“entecavir”[Supplementary Concept] OR “entecavir”[All Fields]) AND ((“lymphoma”[MeSH Terms] OR “lymphoma”[All Fields]) AND (“drug therapy”{Subheading] OR (“drug[All Fields] AND “therapy”[All Fileds]) OR “drug therapy”[All Fields] OR “chemotherapy”[All Fields] OR “drug therapy”[MeSH Terms] OR (“drug”[All Fields] AND “therapy”[All Fields]) OR “chemotherapy”[All Fields])).

From the first literature searching in PubMed, eight articles were found. Seven from eight were English, while the other one written on Chinese language were excluded. The seven remaining articles were appraised by reading the full tect. The choosen article for this EBCR is the one that compared lamivudine and entecavir directly in lymphoma patients undergo chemotherapy. Six article were excluded as they were not fulfill the required criteria. Literature searching algorithm can be seen in Figure 1. Besides PubMed, literature searching was also done in Highwire, Cochrane, and Google Scholar. In Google Scholar searching, on article was found which copared entecavir and lamivudine as hepatitis B prophylaxis in malignancy. Therefore, in this EBCR two multicenter studies were appraised in advanced.

During critical appraisal of those articles, a guide by Polgar A and Thomas SA in ‘Critical Appraisal Skills Programme’ for clinical obsevationa study (cohort, case control, cross sectional) was used.

The first article were found during PubMed literature searching. The author of this article was Li HR with tittle “Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy” from Journal of Viral Hepatitis 2011;18:877 – 883. The second article from *Google Scholar* authored by Chen FW et al with tittle “*Entecavir versus lamivudine for hepatitis B prophylaxis in patients with haematological disease*” pubished by John Wiley & Sons, can be downloaded via doi: 10.1111/liv.125154.2013. Appraisal for both article were shown in Table 2.

Tabel 2. Article appraisal

	Li HR et al, 2011	Chen FW et al, 2013
What is the paper about?		
1. Is the study relevant to the needs of the project?	Yes	Yes
2. Does the paper address a clearly focused issue?	Yes	Yes
• Are the aims of the investigation clearly stated?		
Do I trust it?		
3. Have the authors reflected the current state of knowledge according to an unbiased review of the literature?	Yes	Yes
• Has a sufficiently complete search of the relevant literature been carried out?		
• Is the evidence included which is unfavourable to the authors point of view?		
4. Is the choice of study method appropriate?	Yes	Yes
• Is the study aim clearly stated?		
5. Is the population studied appripriate?	Yes	Yes
• Is an appropriate control group used?		
6. Is confounding and bias considered?	Yes	Yes
• Have all possible explanations of the effect been considered??		
• Were the assessors blind to the different groups?		
• Could selective drop out explain the effect?		
7. Was follow up for long enough?		
• Could all likely effects have appeared in the time scale?	Yes	Yes
• Could the effect be transitory?		
• Was follow up sufficiently complete?		
8. Was dose response demonstrated?	can't tell	can't tell
What did they find?		
9. Are tables/graphs adequately labelled and understandable?	Yes	Can't tell
10. Are you confident with the authors choice and use of statistica methods, if employed?	Yes	Yes
11. What are the result of this piece of research?	Yes	Yes
• Are the authors conclusions adequately supported by the information cited?		
Are the results relevant locally?		
12. Can the result be applied to the local situation?	Yes	Yes
13. Were all important outcomes/results considered?	Yes	Yes
14. Accepted for further use as Type IV evidence?	Yes	Yes

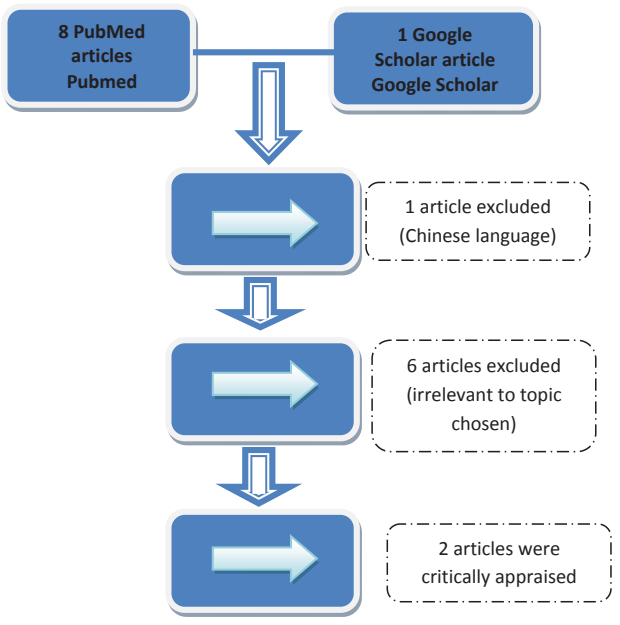

Figure 1. Article selection algorithm in this evidence based case report

RESULTS

In this evidence-based case report, both article found were a retrospective study directly compared entecavir and lamivudine as hepatitis B prophylaxis in chemotherapy. Outcome of those study was HBV reactivation percentage (by assessing HBV DNA value) and HBV infection in both group (by assessing the increase of transaminase). Subject on both study was a hepatitis B patient with either positive or negative HBsAg but positive anti-HBc. There were no differences in characteristic among the two studies. In Li HR et al, all subject were lymphoma patient with almost having cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy agents, while in Chen FW et al, subject were in various hematologic malignancy, although most of the subject is having lymphoma. Dosage used in both study was 100 mg lamivudine and 0.5 mg entecavir.

HBV reactivation defined as the increasing of HBV DNA $\geq$ 1 log10 or the appearance of HBsAg in resolution stage of post HBV infected patients. HBV reactivation could be accompanied by sign and symptoms of hepatitis.[8] Hepatitis was defined as the increasing serum ALT more than three times from normal range, or an absolute ALT increase of more than 100 U/L from baseline. HBV related hepatitis were defined as HBV reactivation in relation with hepatitis during six months post chemotherapy without any sign of acute viral hepatitis or any other systemic infections.[3,7]

Li HR reported an incidence rate of hepatitis (5.9% vs 27%; p = 0.007), stopped chemotherapy cycle because of hepatitis (5.9% vs. 20.2%; p = 0.042), and

HBV related hepatitis (0% vs. 12.4%, p = 0.24) were significantly lower in entecavir groups. Reactivation of HVB were clinically lower in entecavir group than lamivudine group (11.8% vs. 20.2%), but statistically insignificant (p = 0.205).[3] In the study by Chen et al, subject with undetected HBV DNA at the beginning of therapy, both entecavir and lamivudine were effectively the same.[7] Otherwise, in subject with detected HBV DNA at the beginning of therapy, entecavir therapy showed no hepatitis B reactivation, while one from six patient from lamivudine group were having hepatitis B reactivation. This findings could explain that entecavir were more effective than lamivudine. It also can be concluded that lamivudine were still a first line therapy for hepatitis B prophylaxis in HBsAg negative and immune control phase with undetected HBV DNA patients. Entecavir should be saved for patients with detected HBV DNA (immune tolerant phase, immune clearance phase, or eAg negative) because of the lower risk of drug resistance. A little number of sample is one of the weakness of this study.

Study by Li HR et al conclude that reactivation prophylaxis for hepatitis B were based on cancer stadium occurred.[3] In the early stage cancer or patients with short duration chemotherapy, lamivudine still a drug of choice for hepatitis B reactivation prophylaxis. On the other hand, patients with advanced stage cancer or patients required long duration of chemotherapy, entecavir should be the drug of choice. Comparison of both Li et al and Chen et al study result were shown in table 3.

DISCUSSION

HBV chronic infection were marked as detected HBsAg. Chronic HBV infection were having four stages: immune tolerant phase, immune clearance phase, immune control phase (inactive carrier status), and immune escape phase.[9] A few recent years showed that hepatitis B reactivation were found in chemotherapy patients.[3] Hepatitis b reactivation were a life-threatening complication that infect patients with malignancy during chemotherapy.[6] In immunocompromised patients, resolute HBV could be reactivated too. Resolute infection marked as anti-HBc detected without anti-HBs.[7] HBV reactivation prevention could reduce mortality of HBV infection and could reduce chemotherapy dosage caused by HBV reactivation.[10]

Lamivudine were HBV reactivation prophylaxis that recommended in many guidelines. Patients with HBV reactivation risk recommended to start antiviral therapy a week before chemotherapy, continued to the next 6 months after chemotherapy finished.[11] lamivudine were formerly known as the only nucleoside analog to treat chronic hepatitis B infection.[3] lamivudine act as inhibitor of virus replication effectively reduce HBV DNA level and reduce hepatic damage due to chronic hepatitis B infections.[7] The role of lamivudine as prophylaxis has been widely proofed in various clinical trial and was recommended in many guidelines. Otherwise, lamivudine as long term hepatitis therapy were restricted as recently found a hepatitis B virus that is resistance to lamivudine.[3] Long term use of lamivudine for hepatitis B was known to cause drug resistance and hepatitis exacerbation.[12,13] Lamivudine was having a higher mutation rate, about 20% in one year and increase to 70% in 5-years therapy. In this case, hepatitis B reactivation could occur even patient have got lamivudine therapy before.[3]

Entecavir were HBV DNA polymerase inhibitor selective that have an ability to inhibit viral replication, optimize histologica repair, reduce chronic hepatitis B progression, and lower resistance rate rather than lamivudine.[7] As this reason, entecavir were widely used as chronic hepatitis B therapy in Japan, replacing lamivudine since 2000.[13,14] But, there were few studies to investigate its effect as hepatitis B reactivation prophylaxis in chemotherapy patients. Previous study only investigate entecavir role as therapeutic drugs for hepatitis B reactivation in chemotherapy patients.

Choosing the best prophylaxis therapy for hepatitis

Tabel 3. Comparison of study by Li HR et al and Chen FW et al

Parameter	Li et al	Chen et al
Study design	Retrospective cross sectional	Retrospective cross sectional
Population	Patients with lymphoma malignum with positive of either HBsAg, HBeAb, HBeAg or antiHBc.	Patients with cancer or other hematologic malignancy with either positive or negative HBsAg but positive anti-HBc
Intervention	Lamivudine 100 mg, entecavir 0.5 mg	Lamivudine 100 mg, entecavir 0.5 mg
Parameter	HBV reactivation, HBV related hepatitis, stopped chemotherapy because of hepatitis	HBV reactivation, hepatitis, HBV related hepatitis
Result	HBV reactivation rate, HBV related hepatitis, and stopped chemotherapy because of hepatitis shown to be lower in entecavir group	Entecavir were more effective in detected HBV DNA subjects. In undetected HBV DNA subjects, entecavir were as effective as lamivudine

B reactivation could be a problem for hepatologist and hematologist. This choice were based on patients preference. There were no meta-analysis or systematic review found to discuss about lamivudine and entecavir as prophylaxis in chemotherapy patients. Recent study only a retrospective study and only said that entecavir could be used as prophylaxis therapy for hepatitis B reactivation during chemotherapy.[6,8,15]

Critical appraisal on article shown a nearly the same effect on chemotherapy patients with formerly resolute hepatitis B infection. Entecavir were proofed to be more effective in patients with positive HBsAg.[7] Patients with negative HBsAg and positive anti-HBc were a sign of HBV infection resolution. If we apply Chen FW et al study result into this case, entecavir were choosen as therapy rather than lamivudine.[7] Patients in this case is a stage IV lymphoma with lung metastasis shoud be undergo a long term chemotherapy. Based on Li HR et al, entecavir were a first choice for advanced malignancy, so that this patients should get an entecavir therapy as hepatitis B reactivation prophylaxis.[3] But, there were not enough evidence yet to support that conclusion. Study which compared entecavir and lamivudine effectiveness in chemotherapy patients were found in a little number and proposed a small number of sample. As a consequence, it needs more study that compared both of therapy directly to get the more adequate conclusion.

Besides of its minimal study conducted, entecavir use in this case also facing a problem. Although both entecavir and lamivudine were found in Indonesia, entecavir were slightly more expensive in price and not financed by national health insurance. There should be a study about cost-effectiveness between lamivudine and entecavir for HBV prevention. So, it can be concluded that lamivudine still the drug of choice for HBV reactivation prophylaxis until chemotherapy end in this case. Based on various guidelines, lamivudine in this case will be continued to the next six months after chemotherapy finished.

CONCLUSION

From both of the study, it can be concluded that entecavir were more effective than lamivudine in positive HBsAg patients or in advanced stage malignancy patients undergo chemotherapy. Since entecavir cost was unaffordable, lamivudine still be a drug of choice in this case.

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