Reactivation of Hepatitis B Virus Associated with Chemotherapy and Immunosuppressive Agent

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INTRODUCTION

Hepatitis B virus (HBV) reactivation can occur in chronic hepatitis B patient. This issue should be put into account due to serious condition that can lead to fulminant hepatitis, liver failure, and eventually death. Complete HBV serology profile should be screened in patient who will undergo cytotoxic chemotherapy and immunosuppressive therapy. It has been known that preemptive antiviral therapy is more effective than treatment of HBV reactivation.

Key words: hepatitis B virus reactivation, chemotherapy, immunosuppressive.
HEPATITIS B VIRUS

Hepatitis B virus is a double-stranded DNA virus in the Hepadnaviridae family. HBV virion are double-shelled particles, 40 to 42 nm in diameter, with an outer lipoprotein envelope that contains three related envelope glycoproteins (surface antigens). The core contains the viral genome and a polymerase for the viral DNA synthesis in infected cells.¹

PATHOGENESIS OF HEPATITIS B

Host immune responses to viral antigens on infected hepatocytes are the main mechanism of hepatocellular injury.² These responses involve both major-histocompatibility-complex (MHC) class II–restricted, CD4+ helper T cells and MHC class I–restricted, CD8+ cytotoxic T lymphocytes. Recognition reaction of antigen and antigen presenting cell (APC) can lead to either direct lysis of the infected hepatocyte or the release of interferon-γ (IFN-γ) and TNF-α, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.³

Natural history of chronic hepatitis B infection depends on the age at the time of infection and the immune response between host immunity and viral replication. Patient who failed to recover from acute infection will lead to chronic infection through 4 phase: immune tolerance, immune clearance, non-replicative, and reactivation phase.¹

HBV reactivation is related to serologic profile and intensity of immunosuppressive agent.⁷ The pathogenesis of HBV reactivation is still unclear. The use of chemotherapy and highly immunosuppressive agent will markedly suppress the immune response hence increasing the viral load and if the agent was ceased, there will be a fast recovery of immune response and massive cytolitic of infected hepatocytes.⁸

HEPATITIS B VIRUS REACTIVATION

HBV reactivation is a liver necroinflammation in inactive carrier or resulation phase patient. Clinical symptoms are variable from asymptomatic to liver decompensated and death.⁶ HBV reactivation is related to serologic profile and intensity of immunosuppressive agent.⁷ The pathogenesis of HBV reactivation is still unclear. The use of chemotherapy and highly immunosuppressive agent will markedly suppress the immune response hence increasing the viral load and if the agent was ceased, there will be a fast recovery of immune response and massive cytolitic of infected hepatocytes.⁸

EPIDEMIOLOGY

Approximately 2 billion people worldwide have been infected with HBV during their lifetime, with >350 million remaining chronically infected, leading to terminal liver disease or hepatocellular carcinoma which accounts for 1 million of death annually. Approximately 45% of population are in HBV endemic area.⁴
the key of viral replication and can be used for predicting HBV reactivation in HBsAg (+) patient receiving chemotherapy.\(^\text{12}\)

**Patient with HBsAg (-).** Patient with HBsAg (-), anti-HBc (+) and undetectable HBV-DNA, ALT and HBV-DNA must be evaluated and treated with nucleoside analog despite of ALT level.\(^\text{13}\) HBV reactivation in patient with HBsAg (-) but anti-HBc & anti-HBs (+) and in patient with occult anti-HBc is an uncommon condition therefore it is not recommended for routine antiviral prophylaxis. This patient should be evaluated and treated if HBV-DNA is detectable.\(^\text{6}\)

A separate study in Taiwan by Chen et al. has shown that 6% of their HbsAg (-) patients with B-cell lymphoma had occult HBV infection.\(^\text{13}\) In a cohort study by Hui et al. of HBsAg (-) hematopoietic stem cell transplant donors in Hong Kong, the prevalence of occult HBV infection was 15.3%.\(^\text{14}\)

**HBV Reactivation Related to Immuno-suppressive Agent**

**Corticosteroid.** HBV replication increases in the presence of corticosteroids. The peak rise in aminotransferases typically occurs 4-6 weeks after withdrawal. The mechanisms are unclear, maybe due to a glucocorticoid responsive element in the HBV genome that stimulates viral replication and transcriptional activity.\(^\text{15}\)

Study by Cheng et al. found that a steroid-free

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<td>Thioguanine</td>
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<td>Corticosteroids</td>
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<td>Immunotherapy</td>
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<td>Infliximab (anti-TNF)</td>
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<td>Plant Alkaloids</td>
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<td>Vinblastine</td>
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<td>Interferon alpha</td>
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chemotherapy regimen reduced the risk of HBV reactivation in patients with lymphoma.\textsuperscript{16}

**Monoclonal Antibody.** Lymphoid malignancies and immunologic conditions often includes the use of monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52) which are highly immunosuppressive.\textsuperscript{1} Rituximab plus CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is now a standard treatment of diffuse large B-cell lymphoma (DLBCL).\textsuperscript{15} Before preemptive anti-HBV therapy is widely used, treatment of HBsAg (+) lymphoma with CHOP chemotherapy alone is associated with an approximately 50% risk of HBV reactivation, the risks are greater by adding Rituximab.\textsuperscript{17}

**Anti-TNF-α.** Flares of hepatitis have been described during treatment with anti-TNF-α agents in chronic HBV patients with rheumatoid arthritis. Severe flares have also been described in association with methotrexate, particularly following its withdrawal.\textsuperscript{18}

**Bone Marrow Transplantation.** Patient with HBsAg (+) who undergo allogenic bone marrow transplant is in highly immunosuppressive condition and has higher risk of HBV reactivation (14%-50%). Known risk factors are steroid used, anti-HBs (-) donor, and graft-versus-host disease.\textsuperscript{1} In graft-versus-host disease, high dose steroid or antithymocyte globulin (ATG) are needed which suppress the immune system.\textsuperscript{19} Immunization of HBV is recommended for donor and recipient who has never been infected by HBV.\textsuperscript{20}

**Renal Transplantation.** There has been a report about declining of renal graft function in patient receiving adefovir. Entecavir is drug of choice in patient undergoing renal transplant.

**DIAGNOSIS**

Currently, no uniform diagnostic criteria are available for HBV reactivation. HBV reactivation can be confirmed by an increase in serum HBV-DNA level to more than 1 log higher than that of the baseline, an absolute increase exceeding 6 log10 copies/mL, or serum HBV-DNA turning from negative to positive. Serologic evidence of chronic HBV infection would be useful. Commonly, elevation of HBV-DNA happens prior to elevation of transaminase. As reactivation may be transient, more frequent HBV-DNA and ALT monitoring will lead to a higher rate of diagnosis.\textsuperscript{10}

**TREATMENT**

When a clinical diagnosis is made, chemotherapy and potential hepatotoxic agent must be ceased and treatment is based on antiviral and supportive care.\textsuperscript{1} Lamivudine, a nucleoside analog, is an effective treatment of chronic HBV infection. The drug is active in controlling viral replication and is therefore potentially useful for the treatment of HBV reactivation. Good prognosis can be estimated if lamivudine is given at the time of HBV-DNA elevation.\textsuperscript{21} There is a report about the successful of emergency liver transplantation in heterologous bone marrow transplantation patient with fulminant HBV reactivation.\textsuperscript{22}

**PROGNOSIS**

HBV reactivation is related to long-term declining of liver function. Eventhough some patients can have spontaneous recovery, mortality rate occurs in about 5% - 40%. Patient with anti-HBc (+) has lower risk of reactivation compared to patient with HBsAg (+), but mortality rate is higher in patient with anti-HBc (+). Mortality rate is still high although already been treated with antiviral because usually the viral load is already high and massive immune-mediated hepatocytes injury has already occured.\textsuperscript{23}

**PROPHYLACTIC**

All chemotherapy and immunosuppressive candidates should be screened for HBsAg and anti-HBc before receiving the treatment.\textsuperscript{1} There are currently two approaches in management
of patients at risk, namely treatment of HBV reactivation when it is diagnosed, and prevention through preemptive treatment prior to or upon initiation of chemotherapy. Preemptive antiviral therapy was the best approach to prevent the reactivation.

American Association for the Study of Liver Diseases (AASLD) 2009 consensus recommend prophylactic antiviral therapy for HBV carriers at the onset of chemotherapy or of a finite course of immunosuppressive therapy.

European Association for the Study of the Liver (EASL) 2009 consensus also recommend about HBV vaccination in seronegative patient and evaluate HBV-DNA level before starting chemotherapy and receiving preemptive therapy along and continue to at least 12 months after chemotherapy.

Asia Pacific Association for The Study of the Liver (APASL) 2008 consensus recommend lamivudine as preemptive therapy for chemotherapy candidates, starting 1 week prior to and continue to at least 12 week after chemotherapy.

Perhimpunan Peneliti Hepatologi Indonesia (PPHI) 2006 consensus also recommend lamivudine therapy before administer chemotherapy or immunosuppressive agent and should be continue at least 6 weeks after treatment.

Metaanalysis study by Ziakas et al. reveals that in 9 trials, cumulative prevalence for HBV reactivation in prophylaxis group was 8.6% compared to 50.6% in control group. The incidence for those who did not receive prophylaxis therapy are 54.5%-100%.

For patient receiving monoclonal antibody treatment, antiviral therapy should be given for at least 12 months because of slow immune recovery.

HBV reactivation can be happened in those who already received lamivudine, this maybe due to drug resistency because of YMDD (tirosin-metionin-aspartat) mutant. Others nucleoside analog like adefovir, entecavir, telbivudine, and tenofovir, can be given to those with lamivudine-resistant.

**CONCLUSION**

HBV reactivation is a common complication in patient receiving chemotherapy and immunosuppressive agent, therefore we should be aware regarding its serious implication. Patient

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**Figure 4.** Screening algorithm and prophylaxis of HBV reactivation

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*Currently recommended first line treatment: lamivudine 100 mg/d. For YMDD mutant consider adefovir or entecavir.*
with malignancy in HBV endemic area should be screened routinely for hepatitis B status before receiving cytotoxic chemotherapy. Preemptive therapy with nucleoside analog had significantly reduced the incidence, morbidity, and mortality of HBV reactivation.

REFERENCES


