Hepatitis B Reactivation in Immunosupressed Patients, Prophylaxis and Management

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ABSTRACT

Hepatitis B virus (HBV) reactivation is a clinical problem associated with high morbidity and mortality rates. Currently, this incidence seems to be increasing around the world. The reactivation commonly developes in immunosuppressed individuals, although it may also occur spontaneously. Individuals who develop malignancy with chronic hepatitis B virus infection are at high-risk for hepatitis B virus reactivation, since they are closely related to immunosuppression, especially when undergoing chemotherapy. The loss of immune control in these patients may results in the reactivation of HBV replication within hepatocytes. This review article will focus on HBV reactivation related to immunosuppressed patients, immunosuppressive drug classes and corresponding risk estimates of hepatitis B virus reactivation, screening test recommended before getting this drugs, choice of antiviral drugs for prophylaxis, and duration of prophylaxis treatment based on European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and Asian Pacific for the Study of the Liver (APASL) guidelines.

Keywords: *hepatitis B reactivation, immunosuppresive, chemotherapy, prophylaxis, treatment*

ABSTRAK

Reaktivasi hepatitis B adalah merupakan masalah klinis dengan morbiditas dan mortalitas yang tinggi. Akhi-akhir ini angka kejadian reaktivasi virus hepatitis B (VHB) tampak meningkat di seluruh dunia. Reaktivasi VHB sangat sering terjadi pada individu dengan kondisi imun tersupresi, walaupun juga bisa terjadi secara spontan. Individu yang mempunyai penyakit keganasan dan hepatitis kronis B mempunyai risiko tinggi untuk terjadi reaktivasi VHB, khususnya jika menjalani prosedur khemoterapi. Mekanisme yang mendasari terjadinya reaktivasi adalah hilangnya kontrol imun atas replikasi VHB di hepatosit. Review artikel ini akan membahas tentang reaktivasi VHB terkait imunosupresan, jenis kelas obat-obat imunosupresan apa saja yang mempunyai risiko dan prediksi besarnya risiko terjadinya reaktivasi VHB, pemeriksaan yang diperlukan untuk skrining pada pasien-pasien sebelum menjalani kemoterapi, pemilihan jenis antiviral dan berapa lama pemberian terapi profilaksis untuk mencegah terjadinya reaktivasi VHB dari berbagai guideline yang dikeluarkan oleh European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), dan Asian Pacific for the Study of the Liver (APASL).

Kata kunci: *reaktivasi hepatitis B, imunosupresif, kemoterapi, profilaksis, terapi*

INTRODUCTION

Hepatitis B virus is a DNA virus which could lead to potentially life-threatening liver infection.[1] Hepatitis B virus infection is a major public health problem worldwide that needs special concern. Roughly 30% of the world's population show serological evidence of current or past infection.[2] Approximately 350-400 millions people live with chronic infection. An estimated 600.000 people die each year due to the acute or chronic consequences of hepatitis B virus infection.[1]

Chronic hepatitis B virus infection could lead to progressive liver damage, but mostly (60-85%) are asymptomatic. That is why it becomes undetectable, until signs and symptoms of chronic liver disease/cirrhosis appear.[2] However, hepatitis B virus reactivation in this population may occur, either spontaneously or upon immunosuppression. Impairment of the host immune system due to treatment with chemotherapeutic or immunosuppressive agents raises the risk of HBV reactivation. The consequences of hepatitis B virus reactivation range from self-limited conditions to fulminant hepatic failure and death.[4,5]

HEPATITIS B VIRUS REACTIVATION

Hepatitis B virus reactivation is a sudden increase of hepatitis B virus DNA (more than 10-fold) in serum, or reappearance of hepatitis B virus DNA in the serum, commonly accompanied by increase of alanine transaminase (ALT) level in patient with inactive or resolved hepatitis B. The increase of ALT level is characterized by threefold rise above the upper limit of normal value or an absolute increase more than 100 U/L. Also, previously HBeAg-negative patients become HBeAg-positive. To diagnose hepatitis attributed to hepatitis B virus reactivation, clinicians must exclude other possible causes, such as evidence of hepatic infiltration by underlying malignancy, administration of hepatotoxic drugs, recent history of transfusion, and presence of other systemic infections. For patients with HBsAg-negative and HBcAg-positive, hepatitis B virus reactivation is characterized by reappearance of HBsAg with the increase of ALT level in two measurements over a period of 5 days, and increase of hepatitis B virus DNA more than 10^5 copies/mL.[4,5,6]

Hepatitis B reactivation has been described as a three-phase event (Figure 1). Initially, an increased HBV DNA levels in an HBsAg positive person is found, or reappearance of either HBsAg (seroconversion) or HBV DNA occurs; this period is usually asymptomatic. When the following phase takes places, HBV DNA levels show a sustained increase in viral load, accompanied by concomitant elevations in aminotransferase levels, which may also be associated to the development of severe hepatocellular damage; to note, even acute liver failure and ultimately death may occur. The aforementioned events result from a reconstitution syndrome of the host immune response. Finally, liver damage resolves due to recovery of the immune system strength (spontaneously or as a result of immunosuppressive therapy suspension) or due to administration of antiviral drugs. [2]

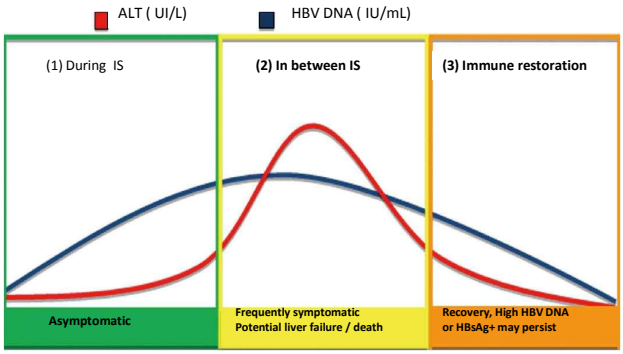

Figure 1. Hepatitis B reactivation phases. In the initial phase, there is an increase in HBV DNA levels, usually with an asymptomatic evolution. In the second phase,both ALT and HBV DNA are elevated; symptoms are frequently present, and they may be severe. The third phase is determined by resolution, although HBsAg (if reappeared), or elevated HBV DNA, may persist. IS: Immunosuppression; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface Antigen [2]

The causes of hepatitis B virus reactivation are varied, although this could be spontaneous, in most patients who develop viral reactivation, due to imbalance between host immunity and hepatitis B virus activity. This imbalance may be induced by immunosuppressive agents, cytotoxic chemotherapy, HIV infection, or sudden withdrawal of antiviral therapy.[4] Clinically, hepatitis B virus reactivation varies from asymptomatic elevation of serum ALT to acute liver failure and death.[1]

CHEMOTHERAPY-RELATED REACTIVATION OF HEPATITIS B VIRUS INFECTION

Malignant cancer is a worldwide disease and in developing countries one in three people will develop cancer during their lifetimes.[7] Over the last decades, chemotherapy has demonstrated a significant role in malignancy treatment and may prolong life expectancy. It is estimated that 1 in 4 patients with malignancy and chronic hepatitis B infection in Japan develop infection reactivation due to receiving chemotherapy. Hepatitis

B virus reactivation during anticancer treatment may results in life-threatening events and poor outcome due to early discontinuation of chemotherapy.[6,8]

The first prospective study on hepatitis B virus reactivation was published in 1991, and included Chinese patients with malignant lymphoma who received chemotherapy. Hoofnagle et al described 2 cases of hepatitis B virus reactivation in asymptomatic hepatitis B virus carriers within 3 months of starting chemotherapy. Several other studies have shown that the median interval between the initiation of chemotherapy and the onset of reactivation was 4 months (1–9 months). The rate of hepatitis B virus reactivation in patients with chronic hepatitis B virus infection who have positive serum HBsAg ranges from 24–88%, and in patients who are anti-HBc-positive ranges from 3–22%. The mortality rate in HBV reactivation ranges from 23–71%.[1]

Usually, HBV viral loads increase when patients receive immunosuppressants or chemotherapy. After withdrawal of such treatments, the host immune response rebounds, and hepatitis flare develops.[4] This viral replication occurs after the start of chemotherapy due to suppressed cellular immune response, the spread of hepatitis B virus to hepatocytes and rising serum hepatitis B virus DNA levels. These modifications may occur up to three weeks earlier than laboratory alterations and may be accompanied by serological reappearance of HBeAg and HBsAg. After chemotherapy withdrawal, the immunological function of host is restored leading to cytotoxic-T-cells mediated destruction of hepatitis B virus infected hepatocytes. This results in increasing ALT levels (hepatic flare) and may cause several clinical manifestations that could range from mild to severe, such as fulminant hepatic failure or even death.[5,8] During this phase, HBV DNA levels may decrease.[8]

The risk factors for hepatitis B virus reactivation have not been clearly identified. The key to prevent HBV reactivation is the timely identification of HBV-infected patients prior to immunosuppressive therapy. Risk factors associated with HBV reactivation have been less described. Risk factors for HBV reactivation in patients with current/past hepatitis B infection are included in Table 1.[2]

Most of the risk factors identified to date are based on case studies of small sample size. Hepatitis B virus reactivation usually occurs after the second or third course of chemotherapy [1]. Several clinical predictors of hepatitis B virus reactivation have been identified, including a certain serum HBV DNA level prior to immunosuppression, the type of underlying malignancy, the regimen of chemotherapy, and the intensity of immunosuppression. Generally, risk factors for anticancer chemotherapy-related hepatitis B virus reactivation could be divided into several categories as follows, host factors, type of malignancy or treatment-related factors, as well as viral factors.[3] Studies conducted by Yeo et al and Matsue et al showed risk factors for *h*epatitis B virus reactivation in patients with negative HBsAg/positive HbcAb, especially related to male gender and rituximab use and negative anti-HBs.[5]

Table 1. Risk factors for anticancer chemotherapy-related hepatitis B virus reactivations[3,5]

Categories	Risk factors
Host factors	Male gender
	Young age
	Elevated baseline ALT
Tumour- or treatment-related factors	Lymphoma
	Haematological malignancies
	Breast cancer
	Glucocorticoid use
	Anthracycline use
	Rituximab-based regimen
	Hematopoietic stem cell transplantation
	TACE treatment for HCC
Viral factors	High pre-chemotherapy viral load
	Positive HBeAg
	Presence of precore mutant
	Negative or low titre of HBsAb (in case of occult/past infection)

CHEMOTHERAPEUTIC AGENTS ASSOCIATED WITH HEPATITIS B VIRUS REACTIVATION

Various types of chemotherapeutic agents may cause immunosuppressive state in patients that could induce hepatitis B virus reactivation in patients with chronic hepatitis B infection. Table 2 summarizes various types of chemotherapeutic agents that have been reported to cause hepatitis B virus reactivation.[1]

Those chemotherapeutic agents listed in Table 2 have different magnitude of risk for hepatitis B virus reactivation in patients with positive HBsAg and negative HBsAg/positive anti-HBc. Several new chemotherapeutic agents (biological agents) such as B-cell depletion agents are potent immunosuppressants, that yield higher risk for hepatitis B virus reactivation. For instance, rituximab, is an agent predominantly used to treat haematological malignancy in addition to autoimmune and neurological disease.[9,10] Rituximab is an agent that works against CD20 on B-cell. CD20 positive B-cells depletion might reduce the number of CD4 memory cells, CD8 cells, and antibody-mediated immunity. It results in acceleration of hepatitis B virus replication during receiving rituximab-based chemotherapy. Rituximab-based chemotherapy has been reported to cause hepatitis B reactivation even

when administered alone or even in combination. The rate of hepatitis B virus reactivation during rituximab treatment when combined with chemotherapy has been reported to be 20-55% overall and 3% in patients with negative HbsAg.[10,11]

Table 2. Chemotherapeutic agents associated with hepatitis B virus reactivation[1]

Class	Name of drugs
Alkylating agents	Chlorambucil, Cyclophosphamide, Ifosfamide, Mercaptopurine
Anthracyclines	Doxorubicin, Daunorubicin, Idarubicin, Epirubicin
Antimetabolite	5-Fluorouracil, Methotrexate, Cytarabine, Gemcitabine
Antitumor antibiotic	Actinomycin-D, Bleomycin, Mitomycin-C
Corticosteroids	Prednisone, Dexamethasone, Methylprednisolone
Platinum	Cisplatin, Carboplatin
Taxane	Paclitaxel, Docetaxel
Vinka Alkaloid	Vincristine, Vinblastine
Other cytotoxic agents	Etoposide, Procarbazine, Dacarbazine, Lomustine
Biologicals	Rituximab, Alemtuzumab
Tyrosine kinase inhibitor	Imatinib
Immune modulator	Interferon, Thalidomide

Corticosteroids are the most commonly used immunosuppressants associated with hepatitis B virus reactivation through their effect on T-cell function, that also may enhance hepatitis B virus replication through their interaction with the hepatitis B virus glucocorticoid element (a transcriptional regulatory element). A study has demonstrated that a 4-weeks course of prednisone has been associated with hepatitis B virus reactivation in the post-withdrawal phase of prednisone and worsened liver histology. The rate of hepatitis B virus reactivation events in the setting of chronic airways disease due to chronic oral vs. inhaled steroid use is 11.1% and 3.2%, respectively.[9] The magnitude of risk of hepatitis B virus reactivation due to various chemotherapeutic/ immunosuppressive agents are shown in Table 2 and Figure 3.

Patients undergoing stem cell/bone marrow transplantation are at the highest HBVr-risk followed by those receiving solid organ transplantation. Bone marrow/stem cell transplanted patients typically need intense chemotherapy to induce remission of the underlying malignancy, followed by additional chemotherapy and radiation therapy to ablate bone marrow. This setting causes the rate of hepatitis B virus reactivation reaches 50% in both HBsAg-positive and HBsAg-negative with anti-HBc-positive patients. Anti-HBs titres below 10 mUI/mL are a predictor of HBsAg seroreversion in the group of patients with HBsAg-negative/anti-HBc-positive.[2]

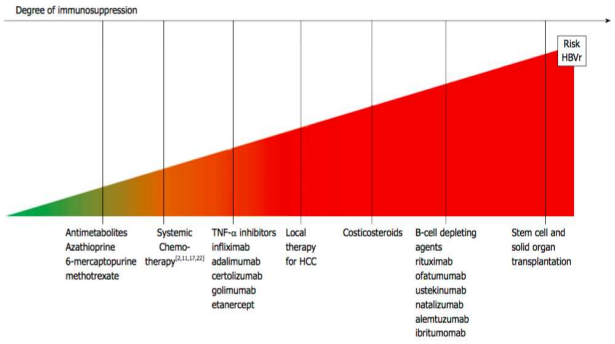

Figure 2. Immunosuppressing agents and related risk of hepatitis B reactivation[2]

*)Hepatitis B reactivation during administration of immunosuppressant agents with low doses of azathioprine or methotrexate as monotherapy is uncommon. In a recently published review, no report was found in which azathioprine user alone was documented to causa hepatitis B reactivation. Similarly, although report associated with methotrexate-induced hepatitis B reactivation are available, most of them involved the concomitant use of other imunomodulator (2)

*)Tumour necrosis factor a (TNF-α) is a pro-inflammatory and immunoregulatory cytokine involved in the patoghenesis of seberat inflammatory disorder. The inhibition of TNF-α signalling can lead to increased HBV replication and reactivation. ;

Table 3. Immunosuppressive drug classes and corresponding risk estimates of hepatitis B virus reactivation[9]

Drug class	Drug	Risk estimate of HBVr for HBsAg +	Risk estimate of HBVr for HBsAg-/anti-HBc +
B-cell depleting agents	Rituximab (anti-CD20) Ofatumumab (anti-CD20)	High (30-60%)	High (>10%)
Anthracycline derivatives	Doxorubicin Epirubicin	High (15-30%)	High (>10%)
TNF-α inhibitors	Infliximab Etanercept Adalimumab	Moderate (1-10%)	Moderate (1%)
Cytokine inhibitors and integrin inhibitors	Abatacept (anti-CD80,-86) Ustekinumab (anti IL12,-23) Natalizumab (bind α4-integrin) Vedolizumab (bind integrin α4β7/LPAM-1)	Moderate (1-10%)	Moderate (1%)
Tyrosine kinase inhibitors	Imatinib Nilotinib	Moderate (1-10%)	Moderate (1%)
Corticosteroids	High dose, e.g. prednisone ≥20mg for ≥4wk Moderate dose, e.g. prednisone <20mg for ≥4wk Low dose, e.g. prednisone <1wk Intraarticular corticosteroids	High (>10%) Moderate (1-10%) Low (<1%) Low (<1%)	Not available Moderate (1-10%) Low(<<1%) Low (<<1%)
Traditional immunosuppression	Azathioprine 6-mercaptopurine Methotrexate	Low (<1%)	Low (<<1%)

PROPHYLAXIS AND MANAGEMENT OF HEPATITIS B VIRUS REACTIVATION

The rate of conversion to fulminant hepatitis as a result of hepatitis B virus reactivation and the mortality rate are estimated higher among patients with hepatitis B virus reactivation than among patients with acute hepatitis. It suggests that the prognosis of patients with hepatitis B virus reactivation who also develop liver damage is extremely poor, thus it is important to suppress reactivation before liver dysfunction is developed.[6] Various ways to prevent hepatitis B virus reactivation in patients receiving immunosuppressive agents such as chemotherapy are required and have already been performed. These include some aspects, such as optimal screening in certain population requiring prophylactic therapy, selection of the most appropriate agent, duration of prophylaxis, type and duration of monitoring in high-risk population of patients who do not receive prophylaxis.[1,12]

Management guidelines originating from America, Europe, and the Asia-Pacific region recommend all cancer patients should be checked hepatitis B virus markers. These markers include HBsAg and anti-HBc, and should be checked prior to initiation of chemotherapy. Prophylactic antiviral therapy is recommended for individuals who are positive for HBsAg before the start of chemotherapy. The duration of antiviral prophylaxis must be extended for at least 6 months after completing chemotherapy to avoid delayed HBV reactivation. It would be better to have a longer duration of antiviral therapy until treatment end points are reached, i.e. HBeAg seroconversion for HBeAg-positive, undetectable level of hepatitis B virus DNA and HBsAg loss for HBeAg-negative patients. It is highly recommended for patients with high viral loads at baseline (>2,000 IU/mL). For cases with low viral load at baseline and treatment duration is less than 12 months, antiviral drugs such as lamivudine or telbivudine could be used. Otherwise, antiviral drugs such as entecavir or tenofovir are preferred.[4,8,12,13]

In HbsAg-positive patients, duration could be determined by clinical indication as in immunocompetent patients. A 12-months treatment was only endorsed by EASL. Drug selection depends on treatment duration and clinical setting. In isolated anti-HBc-positive patients when treated with biologic agents, close follow-up and treatment if necessary, is suggested by AASLD/APASL; however EASL proposes that isolated anti-HBc-positive patients, if HBV-DNA-positive, anti-HBs-negative or undergoing rituximab/stem cell transplantation, should be treated with the same strategy as HbsAg positive patients; When monitored, treatment should start when HBV DNA becomes positive , before ALT rises (EASL); Treatment in all HBV-related HCC patients undergoing TACE is suggested by APASL guideline. Generally, individuals with HBsAg-negative/anti-HBc-positive except transplantation, have no recommendation yet to receive prophylactic antiviral therapy, but should be monitored continuously during chemotherapy to detect reactivation and administer prompt management.[2]

Table 4. Comparison of prophylaxis strategies against hepatitis B reactivation with recent major guidelines[3]

	AASLD (2009)	EASL (2012)	APASL (2012)
Screening tests	HBsAg, anti-HBc	HBsAg, anti-HBc	HBsAg, anti-HBc in rituximab or anti-TNFα-treated patients
Duration of therapy	6 mo after the completion of chemotherapy/ immunosuppression, if baseline HBV DNA <2000 IU/mL; continue treatment until treatment endpoints in immune competent patients if HBV DNA >2000 IU/mL	12 mo after cessation of chemotherapy	At least 24 wk after the end of chemotherapy
Antiviral agent	Lamivudine/Telbivudine if duration of treatment ≤12 mo and baseline HBV DNA is undetectable; tenofovir/entecavir if longer treatment duration is needed	Lamivudine if low HBV DNA (<2000 IU/mL) and a finite, short duration of immunosuppression is planned; entecavir/tenofovir if high HBV DNA and/or lengthy, repeated cycles of immunosuppression are planned	Lamivudine; entecavir/tenofovir can be used
Occult/past infection	Monitor HBV DNA; treat if HBV DNA becomes detectable	Test for HBV DNA; if HBV DNA +, treat similarly for HBsAg + patients; if HBV DNA-negative, follow every 1-3 mo with ALT and HBV DNA and treat upon reactivation before ALT elevation; preemptive therapy can be given if monitoring is not guaranteed or in cases of stem cell transplantation	Monitor HBV DNA; treat when needed

Table 5 : Recommendations for treatment and follow-up in different clinical scenarios, according to APASL, AASLD and EASL guidelines : [2]

recommendation in different clinical scenarios					
	HBsAg (+), HBV DNA > 2000 U/mL	**HBsAg (+), HBV DNA < 2000 U/mL**	**HBsAg(-), antiHBc (+)**	**HBsAg (-), antiHBc (-), antiHBs (-)**	**HBV-HCC TACE**
Action	Treat	Treat	Closed monitor Treat if HBV DNA (+) or Rituximab/ stem cell transplant	vaccination	Treat
Onset	Before IS	Before IS	Before IS	-	Before IS
Duration	6-12 mo (except CI)	6-12 mo (except CI)	6-12 mo	-	-
Drugs	Short IS : LAM (Ldt) Preferred ETV/TDF	Short IS: LAM (Ldt) (ETV/TDF)	Short IS: LAM (Ldt) (ETV/TDF)	-	LAM (ETV/TDF)
Follow up			Every 1-3mo / treat if HBV (+)	-	-

CI : clinical indication; IS : immunosuppressant, HBsAg : Hepatitis B surface antigen; antiHBc : Hepatitis B core antibody; antiHBs : Hepatitis B surface antibody; HBV : Hepatitis B virus, HCC : Hepatocellular carcinoma, TACE : Transarterial chemoembolization, LAM : Lamivudine, ETV : Entecavir, TDF : Tenofovir, LdT : Telbivudine (only listed as an option in AASLD guideline)

There is no established recommendation for routine antiviral prevention for patients who are negative for HBsAg but positive for anti-HBc. Hepatitis B virus DNA should be checked in this group of patients, and continuous hepatitis B DNA monitoring must be performed to detect hepatitis B reactivation. Antiviral treatment should be started as soon as hepatitis B virus DNA has increased tenfold compared with baseline, and >2000 IU/mL during the course of chemotherapy.[4,8,12,13] Patients who will undergo bone marrow transplantation from non-immune donor are recommended to receive prophylactic therapy, while the recipient of liver graft with positive anti-HBc should receive HBIg in addition to prophylactic therapy.[14]

CONCLUSION

HBV reactivation is a clinical problem associated with high morbidity and mortality rates. HBV Screening before starting immunosuppressive therapy is a key factor to prevent HBV reactivation. Many HBV-infected patients are unconscious of their disease or risk factors. An appeal from scientific societies for physicians to spend enough time to assess patients for HBV risk factors prior to begin immunosuppression therapy is mandatory.

Most management guidelines recommend to check hepatitis B virus markers, such as HBsAg and anti-HBc in those who are to undergo chemotherapy. Prophylactic therapy is recommended before the start of chemotherapy until at least 6 or 12 months after completing chemotherapy or when treatment end points are reached. There is no consensus on the length of prophylactic treatment before the patients are treated with immunosuppressive therapy, and for how long this therapy should be extended once treatment is completed. Choice of antiviral drugs for prophylaxis such as lamivudine, telbivudin, entecavir or tenofovir, depends on viral load and duration or therapy.

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