Prevention of hepatitis B reactivation in patients requiring chemotherapy and immunosuppressive therapy

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Abstract

Hepatitis B virus (HBV) reactivation can lead to severe acute hepatic failure and death in patients with HBV infection. HBV reactivation (HBVr) most commonly develops in patients undergoing cancer chemotherapy, especially B cell-depleting agent therapy such as rituximab and ofatumumab for hematological or solid organ malignancies and that receiving hematopoietic stem cell transplantation without antiviral prophylaxis. In addition, the potential consequences of HBVr is particularly a concern when patients are exposed to either immunosuppressive or biologic therapies for the management of rheumatologic diseases, inflammatory bowel disease and dermatologic diseases. Thus, screening with HBV serological markers and prophylactic or pre-emptive antiviral treatment with nucleos(t)ide analogues should be considered in these patients to diminish the risk of HBVr. This review discusses the clinical manifestation, prognosis and management of HBVr, risk stratifications of cancer chemotherapy and immunosuppressive therapy and international guideline recommendations for the prevention of HBVr in patients with HBV infection and resolved hepatitis B.

Key Words: Hepatitis B virus; Reactivation; Chemotherapy; Immunosuppression; Prevention
INTRODUCTION

Global epidemiology of hepatitis B

Hepatitis B virus (HBV) is a virus containing a DNA genome of 3226 base pairs that can cause a potentially life-threatening liver infection[1,2]. About 2 billion people have been infected with HBV worldwide; of which, 350 million are in chronic infection status[3,4]. HBV is one of the most frequently identified pathogens that lead to acute and chronic hepatitis, acute liver failure and death in East Asia. Three quarters of the HBV carries reside in the Asia-Pacific region[5]. Nevertheless, northern, western and central Europe, North America and Australia are among the lowest prevalence area of chronic HBV infection [hepatitis B surface antigen (HBsAg)-positive, 0.2% to 0.5%] and HBV exposure [HBsAg-negative but hepatitis B core antibodies (anti-HBc)-positive, 4% to 6%], while Eastern Europe, the Mediterranean, Russia, Southwest Asia and Central and South America have higher prevalence rates (2% to 7% chronically infected and 20% to 55% exposed). Southeast Asia, China and tropical Africa have the highest prevalence rates (8% to 20% chronically infected and 70% to 95% exposed)[3].

Patients infected with HBV, either chronic or resolved HBV infection cases, are at risk of HBV reactivation (HBVr) when they undergo chemotherapy. HBVr could occur in patients receiving chemotherapy for hematological malignancies or hematopoietic stem cell transplantation (HSCT) recipients as well as patients receiving treatment for solid tumors such as breast cancer[6]. In HBsAg-positive lymphoma patients undergoing rituximab plus steroid combination chemotherapy and HSCT, HBVr rates could be up to 24% to 88%[7-10]. Increasingly, patients with solid tumors receiving chemotherapy, particularly in breast cancer patients receiving anthracycline-based regimens, are also at risk of HBVr[10].

DEFINITION OF HBVr

The recent American Association for the Study of Liver Diseases (AASLD) recommendation guideline defined HBVr in HBsAg-positive, anti-HBc-positive patients as any of the followings: (1) at least 2 log (or 100-fold) increase in HBV DNA compared to baseline; (2) HBV DNA at least 3 log (or 1000) IU/mL in a patient with previously undetectable HBV DNA level; or (3) HBV DNA at least 4 log (or 10000) IU/mL if baseline level is not available[11]. For HBsAg-negative, anti-HBc-positive patients, HBVr could be defined as: (1) HBV DNA is detectable; or (2) reverse HBsAg seroconversion occurs (reappearance of HBsAg)[11].

CLINICAL MANIFESTATION OF HBVr

The clinical manifestations of HBVr vary from absence of symptoms to liver decompensation and mortality. An abrupt surge in HBV DNA levels without symptoms, elevated aminotransferases, symptomatic hepatitis and acute liver failure were encountered in most of the cases with HBVr by severity[12].
The occurrence of HBVr largely depends on the primary disease requiring chemotherapy or immunosuppressive therapy, host immunity, underlying disease and the immunosuppressive agents used. HBVr may occur as early as within the first 2 wk or up to a year after the cessation of chemotherapy and immunosuppressive therapy. Identifying the risk factors and mechanisms associated with HBVr could help quantify the risk of HBVr and manage the clinical consequences[13].

The clinical course of HBVr could be divided into three stages[14,15]. During the first stage, there is a gradual or abrupt increase in serum levels of HBV DNA in HBsAg-positive patients, reappearance of serum HBsAg in patients previously seronegative for HBsAg or reappearance of serum HBV DNA in patients with undetectable HBV DNA before chemotherapy and immunosuppressive therapy. Symptoms of hepatitis are usually absent and the levels of aminotransferases are not elevated at this stage[6]. During the second stage, serum HBV DNA levels increase persistently with elevated aminotransferases levels. The symptoms associated with hepatitis could be present or absent. In cases with severe hepatitis flare up, hepatic injury could further progress and cause liver failure and even death. These changes could occur during treatment duration of chemotherapy and immunosuppressive therapy or after discontinuation of the treatments and may occur with restoration of the host immunity[6,16]. During the third stage, liver injury could resolve after withholding chemotherapy and immunosuppression agents or administration of antivirals[6].

HBVr could develop during or after discontinuation of chemotherapy and immunosuppressive therapy. For patients undergoing chemotherapy for lymphoma, HBVr usually occurs after the second or third courses of treatments. Among non-Hodgkin’s lymphoma patients receiving rituximab-containing therapy, HBVr could develop after six doses of rituximab and within 1 year after the last dose[17]. Occurrence of HBVr may delay or hamper scheduled chemotherapy or immunosuppressive therapy and result in progression of underlying diseases. A study of patients receiving chemotherapy for breast cancer revealed that early discontinuation of chemotherapy or a delay in the scheduled therapy occurred in about 70% of cases with HBVr, corresponding to the figure of only 33% in cases without HBVr[18].

RISK FACTORS FOR HBVr AND UNDERLYING DISEASES

The main risk factors associated with HBVr could be divided into three categories: (1) host factors; (2) virological factors; and (3) type of immunosuppressive regimen. The host factors include male sex, older age, presence of liver cirrhosis and type of diseases requiring immunosuppression[19,20].

Host factor

Younger age and male gender are among the risk factors for HBVr[20]. On the contrary, another study reported old age as a risk factor[12,21]. It has also been found that patients with older age tend to have more virologic conditions (HBsAg positivity, persistently detectable serum HBV DNA and presence of covalently closed circular DNA in the liver), which increase the risk of HBVr[22,23].

Virological factor

The extent of HBV replication before the start of chemotherapy and immunosuppressive therapy is an important risk factor for HBVr. Patients seropositive for HBsAg are at a higher risk of HBVr than those seronegative for HBsAg and seropositive for anti-HBc. Patients seropositive for HBsAg are at a 5- to 8-fold risk for HBVr[6,24]. In the patients receiving chemotherapy for lymphoma, the prevalence rate of HBVr could be 48% in HBsAg-positive patients, 4% in HBsAg-negative/anti-HBc-positive patients and 0% in HBsAg-negative/anti-HBc-negative patients[12,25]. The liver failure could occur in 7% of HBsAg-positive patients, 2% of HBsAg-negative/anti-HBc-positive patients and 0% of HBsAg-negative/anti-HBc-negative patients[12,25].

Patients with resolved HBV infection (HBsAg-negative, anti-HBc-positive) could have occult HBV infection with persistent detectable HBV DNA[26-28]. The HBVr rate ranges from 8.9% to 41.5% in occult HBV infection patients receiving rituximab-containing chemotherapy in different studies using the definitions of HBsAg seroreversion or detectable HBV DNA[29-31]. In a multicenter, randomized, phase 3 study of 326 diffuse large B-cell lymphoma or follicular lymphoma patients with resolved HBV infection, 27 (8.2%) had HBVr that occurred at a median of 125 d after the first dose of obinutuzumab or rituximab immunochemotherapy. Twenty-five of
Table 1 Immunosuppressive agent classes and corresponding risks of hepatitis B reactivation

| Risk group               | Seropositive for HBsAg and anti-HBc | Seronegative for HBsAg, seropositive for anti-HBc |
|--------------------------|-------------------------------------|--------------------------------------------------|
| High risk (> 10%)        | Anti-CD20 antibodies                | Anti-CD20 antibodies                             |
|                          | Anti-CD52 antibodies                |                                                  |
|                          | Anthracycline derivatives           |                                                  |
|                          | Costimulation inhibitors            |                                                  |
|                          | JAK inhibitors                      |                                                  |
|                          | Moderate-high dose corticosteroid therapy\(^1\) for ≥ 4 wk |                                                  |
| Moderate risk (1%-10%)   | TNF-\(\alpha\) inhibitors          | Anthracycline derivatives                        |
|                          | Integrin inhibitors                 | TNF-\(\alpha\) inhibitors                       |
|                          | IL-12 and IL-23 antibodies          | Integrin inhibitors                              |
|                          | Tyrosine kinase inhibitors          | IL-12 and IL-23 antibodies                       |
|                          | Low dose corticosteroid therapy\(^2\) for ≥ 4 wk | Tyrosine kinase inhibitors                       |
| Low risk (< 1%)          | General immunosuppressive agents (azathioprine, 6-mercaptopurine and methotrexate) | General immunosuppressive agents (azathioprine, 6-mercaptopurine and methotrexate) |
|                          | Corticosteroid therapy\(^3\) for ≤ 1 wk | Moderate-high dose corticosteroid therapy\(^1\) for ≥ 4 wk |
|                          | Intra-articular corticosteroids     | Low dose corticosteroid therapy\(^2\) for ≥ 4 wk |

\(^1\)Corticosteroid therapy: Prednisone (or equivalent); low dose (< 10 mg), moderate dose (10-20 mg), high dose (> 20 mg). anti-HBc: Hepatitis B core antibodies; HBsAg: Hepatitis B surface antigen; IL: Interleukin; JAK: Janus kinase; TNF: Tumor necrosis factor.

232 patients (10.8%) without prophylactic nucleos(t)ides had HBVr while only 2 of 94 patients (2.1%) with prophylactic nucleos(t)ides had HBVr\(^3\). Thus, prophylactic nucleos(t)ides should be used in resolved HBV infection patients receiving rituximab-containing regimens for hematological or rheumatological disease\(^3\).

**Immunosuppressive regimen**

The risk of HBVr could be graded according to the potency of immunosuppression agents used as followed: (1) High risk: HBVr rate of more than 10% (anti-CD20 monoclonal antibodies including rituximab; systemic cancer chemotherapy agents such as doxorubicin); (2) Moderate risk: HBVr rate of 1% to 10% (imatinib, ibrutinib and other tyrosine kinase inhibitors; corticosteroids dosage equivalent to more than prednisone 20 mg daily use for more than 4 wk); and (3) Low risk: HBVr rate of less than 1% (traditional immunosuppressive agents such as azathioprine and methotrexate; corticosteroids use for less than 4 wk) (Table 1)\(^2\).

**UNDERLYING DISEASES**

**Hematologic malignancies**

The studies of chemotherapy-associated HBVr were most often investigated in hematologic malignancies such as non-Hodgkin’s lymphoma\(^7,25,34\). B-cell proliferation and lymphocytes infected by HBV also could be observed in non-Hodgkin’s lymphoma patients seronegative for HBsAg\(^22\). HBVr has been investigated in multiple myeloma patients seropositive for HBsAg or seronegative for HBsAg but seropositive for anti-HBc\(^35-37\). Multiple myeloma patients with immune dysfunction are prone to develop HBVr\(^38\). We recommend antiviral prophylaxis in HBsAg-positive patients from 1 wk before starting immunosuppressive agents and until 12 mo after discontinuation of the agents. We also recommend that patients seronegative for HBsAg but seropositive for anti-HBc on drugs targeting B lymphocytes should be provided with antiviral prophylaxis.
**Solid tumors**
The incidence of HBVr associated with systemic cytotoxic chemotherapy ranged from 20% to 36% in solid tumor patients including breast cancer, lung cancer, hepatocellular carcinoma (HCC) and nasopharyngeal cancer who were seropositive for HBsAg[39]. Severe HBVr may occur in 4.3% of HBsAg-positive patients with solid tumors who received chemotherapy without antiviral prophylaxis[7]. Breast cancer patients undergoing chemotherapy are associated with 25% to 40% incidence of HBVr[18,40]. The HBVr rate associated with breast cancer is higher than that associated with other solid cancers (7% to 29%) because anthracycline and corticosteroids are frequently used[41]. We recommend antiviral prophylaxis in HBsAg-positive patients from 1 wk before starting immunosuppressive agents until 12 mo after discontinuation of the agents. At present there are insufficient data to recommend antiviral prophylaxis in HBsAg-negative/anti-HBc-positive patients.

**HCC**
The incidence of HBVr in patients with HCC ranges between 4% and 67%[12,42]. In fact, HBVr can occur during curative or palliative therapies for HCC such as heptatectomy, local ablation, transarterial chemoembolization, systemic chemotherapy and radiation therapy[43]. In HBsAg-positive patients with HCC who were treated with transarterial chemoembolization, 33.7% had HBVr[43]. Of the patients seronegative for HBsAg and treated with transarterial chemoembolization, 11% developed HBVr[44]. Due to the high incidence of HBVr, we recommend to initiate antiviral therapy in all patients with HBV related HCC undergoing chemoradiation, locoregional or systemic therapy.

**HSCT**
Patients undergoing allogeneic HSCT are at the highest risk of HBVr because of high-dose chemotherapy and potent immunosuppressive agents to prevent the rejection of the graft[6]. In HBsAg-positive patients receiving HSCT, 57.6% developed HBVr[45]. HBVr is also not uncommon in patients seronegative for HBsAg but seropositive for anti-HBc undergoing HSCT, with a rate of HBsAg seroreversion of 20% in a retrospective study[46]. We recommend prophylactic antivirals for patients administered with high-risk therapies such as anti-CD20 antibodies or HSCT recipients.

**Rheumatologic diseases**
The incidences of HBVr in patients with rheumatologic disease such as rheumatoid arthritis could be up to 12.3% in patients seropositive for HBsAg[47] and 3% to 5% in patients seronegative for HBsAg but seropositive for anti-HBc-positive[12,48]. Tumor necrosis factor α inhibitors (e.g., etanercept, infliximab and adalimumab) when administered in rheumatoid arthritis and psoriasis patients seropositive for HBsAg are associated with an HBVr rate of 1% to 10%. On the contrary, the reactivation risk is only around 1% in patients seronegative for HBsAg but seropositive for anti-HBc[49]. Therefore, we recommend that HBV prophylaxis may not be indicated in patients seronegative for HBsAg but seropositive for anti-HBc-positive while they could be monitored for hepatic biochemical flare during immunosuppression.

**Inflammatory bowel disease**
The HBVr rates in patients with inflammatory bowel disease range between 0.6% and 36.0% for patients seropositive for HBsAg[50]. The rate ranges between 1.6% and 42.0% for patients seronegative for HBsAg but seropositive for anti-HBc[50]. With the use of tumor necrosis factor α inhibitors and other biologic agents, HBVr including hepatic failure has been reported[51,52]. We recommend that HBsAg-negative, anti-HBc-positive patients with inflammatory bowel disease treated with tumor necrosis factor inhibitors, biologics or conventional immunosuppressive therapies could be monitored without anti-HBV prophylaxis.

**PREVENTION OF HBVr**

**Strategy of screening**
The strategies of screening for HBV before starting chemotherapy and immunosuppressive therapies vary between the recommendations[53-57]. The patients undergoing these therapies that carry a high or moderate risk of HBVr should be screened for HBsAg and anti-HBc with or without checking anti-HBs. The patients...
seronegative for HBsAg, anti-HBc and anti-HBs could be vaccinated against HBV[13].

Risk stratification of HBVr
The risk of HBVr could be categorized into high risk (> 10%), moderate risk (1%-10%) and low risk (< 1%) according to the risk of reactivation (Table 1)[49,54,58].

High-risk patients (> 10%)
B-cell depleting agents such as rituximab are associated with a high risk for HBVr and thus antiviral prophylaxis should be administered in the patients exposed to HBV regardless of the HBsAg status[59]. These patients should be given prophylactic antivirals (entecavir or tenofovir preferred) before the start of chemotherapy and immunosuppressive treatments[12]. Monitoring for HBVr should continue for another 6 to 12 mo after the cessation of prophylactic antivirals[60].

Moderate-risk patients (1%-10%)
Pre-emptive therapy is defined as antivirals initiated at the rise of serum HBV DNA or alanine aminotransferase (ALT) levels but before the onset of hepatitis symptoms or liver failure. Primary prophylaxis therapy is defined as antivirals started before or at the initiation of immunosuppressive agents and before rise in HBV DNA or ALT levels. In HBsAg-negative and anti-HBc positive subjects with moderate (< 10%) or low (< 1%) risk of HBVr, pre-emptive therapy, instead of prophylactic therapy, is generally recommended[60]. Pre-emptive therapy is based on monitoring HBsAg and/or HBV DNA at 1 to 3 mo intervals during and after immunosuppression and starting antiviral therapy in case of detectable HBV DNA or HBsAg seroreversion[60].

Low-risk patients (< 1%)
Close monitoring of HBsAg, HBV DNA and ALT levels with on-demand antiviral therapy could be offered for the patients who carry a low risk for HBVr.

Screening
Screening of HBV using tests including HBsAg, anti-HBc and anti-HBs should be performed before the initiation of chemotherapy or immunosuppressive agents. Patients seropositive for HBsAg with serum HBV DNA level of equal to or greater than 2000 IU/mL and an increased ALT level should start nucleos(t)ide analogues as recommended by the American Association for the Study of Liver Diseases guidelines [11]. A proposed algorithm of HBVr prophylaxis and treatment for patients receiving chemotherapy and immunosuppressive therapy are described in Figure 1[11,58,60,61].

Given the fact that screening for HBV before chemotherapy and immunosuppressive therapy with prophylactic antiviral agents could significantly decrease the occurrence of HBVr, the screening rates remain relatively low in non-HBV endemic countries such as the United States (17%) and Canada (14% to 31%)[62-64]. A retrospective cohort study from Taiwan, which included 2512 cancer patients receiving chemotherapy, found that a computerized order entry-based alert system (e-REMININDER) and a therapeutic control system (e-CONTROL) achieved a very high pre-chemotherapy HBV screening rate (99.3%) and a high antiviral agents prophylactic rate (95.8%) without any event of severe or acute HBVr (Figure 2)[65].

Optimal Antiviral Agent Prophylaxis
Prophylactic lamivudine significantly decreases the risk of HBVr, hepatitis and mortality in patients undergoing chemotherapy[19,66]. Pre-emptive therapy with lamivudine before the initiation of chemotherapy also decreases the risk of interruption of cancer chemotherapy.

The main concern about lamivudine is that the genetic barrier is relatively low, although it is effective for the prophylaxis of HBVr[19,55]. The resistance rates of lamivudine are 20% and 30% at 1 and 2 years, respectively, and increase exponentially thereafter[55]. In some countries, the use of lamivudine, adefovir and telbivudine (agents with low genetic barriers) may be considered because of the low cost. This is particularly true for patients seropositive for HBsAg with undetectable or very low levels of serum HBV DNA[13]. Entecavir or tenofovir is the agent of choice for the prophylaxis of HBVr because these antivirals have a high genetic barrier[54,55,67]. In a randomized, controlled trial comparing entecavir 0.5 mg daily and lamivudine 100 mg daily in prophylaxis of HBVr in lymphoma patients seropositive for HBsAg receiving
rituximab-containing chemotherapy, entecavir was superior to lamivudine in terms of decreasing the risk of developing hepatitis (0% vs 13.3%), HBVr (6.6% vs 30.0%) and disruption of chemotherapy (1.6% vs 18.3%)[67]. As for the patients undergoing systemic cytotoxic chemotherapy for solid tumors, antiviral prophylaxis reduced the risk for HBVr, HBV-related hepatitis and chemotherapy interruption[68]. Entecavir was superior to lamivudine with less incidence of HBVr in the patients with a baseline HBV DNA level ≥ 2000 IU/mL[39]. A recent meta-analysis revealed that both tenofovir and entecavir could be the most efficacious therapies in the prophylaxis of HBVr[69]. Table 2 summarizes the recommendations for treatment and follow-up in different clinical scenarios and choice of antiviral agents. Most experts recommend routine screening before cancer chemotherapy[70,71].

No standard strategy has hitherto been established to prevent HBVr in patients with resolved HBV infection. A recent meta-analysis with 13 studies showed no association between antiviral prophylaxis and risk of HBVr in patients with resolved hepatitis B [72]. Nevertheless, providing antiviral prophylaxis to the patients receiving rituximab-containing therapy could be considered[72]. Huang et al[27] recently revealed that HBVr and HBsAg seroconversion were not uncommon in patients with lymphoma and resolved hepatitis B, and entecavir prophylaxis could significantly prevent rituximab-associated HBVr[27]. In patients with hematological malignancy and resolved hepatitis B receiving rituximab-containing regimens, tenofovir effectively prevents the occurrence of HBVr[73]. Prophylactic lamivudine may be considered only in the patients without HBV viremia[74].

**CONCLUSION**

HBVr is increasingly recognized as a clinical challenge with a risk of significant morbidity and mortality. Development of HBVr with an increase in serum HBV DNA...
| Recommendations of international guidelines for treatment and follow-up in different clinical scenarios |
|---------------------------------------------------------------|
| **AASLD 2018** | **EASL 2017** | **APASL 2016** | **AGA 2015** |
| Screening before chemotherapy/immunosuppressive therapy | HBsAg and anti-HBc | HBsAg, anti-HBc, and anti-HBs | HBsAg and anti-HBc | HBsAg and anti-HBc |
| Start antiviral prophylaxis before chemotherapy/immunosuppressive therapy | For HBsAg (+) patients | For HBsAg (+) patients | For HBsAg (+) patients | For HBsAg (+) patients |
| Treatment duration of antiviral treatment after completing chemotherapy/immunosuppressive therapy | At least 6 mo | 12 mo | 12 mo | At least 6 mo |
| Antivirals of choice | TDF, TAF or ETV | TDF, TAF or ETV | TDF and ETV | TDF and ETV |

AASLD: American Association for the Study of Liver Diseases; AGA: American gastroenterology association; anti-HBc: Hepatitis B core antibodies; APASL: Asian pacific association for the study of the liver; EASL: European association for the study of the liver; ETV: Entecavir; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.

Figure 2 Modified road map for hepatitis B virus screening before chemotherapy and prophylaxis in the order entry-based screening reminder (e-RENDER) and therapeutic control (e-CONTROL) system (Courtesy of Professor Ping-I Hsu). anti-HBc: Hepatitis B core antibodies; HBsAg: Hepatitis B surface antigen.

and aminotransferases could occur in 20% to 50% of HBV carriers undergoing
cytotoxic chemotherapy for cancer treatment or immunosuppressive therapy with a mortality rate of approximately 5% [75].

Screening for HBV before immunosuppression and chemotherapy is required to prevent the occurrence of HBVr. Screening tests including HBsAg and anti-HBc with or without anti-HBs in the patients about to start anticancer and immunosuppressive therapy is recommended. An integrated strategy involving screening the patients at risk, stratifying the patients for risk according to the status of HBV and the type of immunosuppressive agents administered and careful evaluation of the prophylactic therapy could significantly lower the risk of HBVr.

Entecavir or tenofovir are preferred over lamivudine as antiviral therapy for the prophylaxis of HBVr. The optimal duration of prophylactic antiviral therapy remains to be defined. Current international guidelines suggest administration of prophylactic antiviral therapy for at least 6 to 12 mo after the completion of chemotherapy and even longer for rituximab users or patients with high serum HBV DNA levels before the start of chemotherapy. However, patients with chronic hepatitis B or cirrhosis should continue antiviral therapy regardless of the duration of chemotherapy. Aggressive screening of HBV with adequate antiviral prophylaxis is the optimal strategy for preventing HBVr during chemotherapy and immunosuppressive therapy.

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