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Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies in the targeted therapy era

Mak JWY *et al*. Management of HBV reactivation

Abstract

Hepatitis due to hepatitis B virus (HBV) reactivation can be serious and potentially fatal, but is preventable. HBV reactivation is most commonly reported in patients receiving chemotherapy, especially rituximab-containing therapy for hematological cancers and those receiving stem cell transplantation. Patients with inactive and even resolved HBV infection still have persistence of HBV genomes in the liver. The expression of these silent genomes is controlled by the immune system. Suppression or ablation of immune cells, most importantly B cells, may lead to reactivation of seemingly resolved HBV infection. Thus, all patients with hematological malignancies receiving anticancer therapy should be screened for active or resolved HBV infection by blood tests for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen. Patients found to be positive for HBsAg should be given prophylactic antiviral therapy. For patients with resolved HBV infection, there are two approaches. The first is pre-emptive therapy guided by serial HBV DNA monitoring, and treatment with antiviral therapy as soon as HBV DNA becomes detectable. The second approach is prophylactic antiviral therapy, particularly for patients receiving high-risk therapy, especially anti-CD20 monoclonal antibody or hematopoietic stem cell transplantation. Entecavir or tenofovir are the preferred antiviral choices. Many new effective therapies for hematological malignancies have been introduced in the past decade, for example, chimeric antigen receptor (CAR) T-cell therapy, novel monoclonal antibodies, bispecific antibody drug conjugates, and small molecule inhibitors, which may be associated with HBV reactivation. Although there is limited evidence to guide the optimal preventive measures, we recommend antiviral prophylaxis in HBsAg-positive patients receiving novel treatments, including the Bruton tyrosine kinase inhibitors, B-cell lymphoma 2 inhibitors and CAR-T cell therapy. Further studies are needed to determine the risk of HBV reactivation with these agents and the best prophylactic strategy.

Key Words: Hepatitis B; Hematologic neoplasms; Chimeric antigen receptor-T cell therapy; Monoclonal antibodies; Bruton's tyrosine kinase inhibitors; Antiviral agents

Core Tip: Patients with chronic or past resolved hepatitis B virus (HBV) infection are at risk of reactivation of the virus when they receive chemotherapy or immunosuppressive therapy. Therefore, before treatment, patients should be screened for HBV markers, specifically hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen. Prophylactic antiviral therapy is important for HBsAg-positive patients, and is a reasonable option for patients with resolved HBV infection who are scheduled to receive high-risk therapy such as anti-CD20 monoclonal antibodies, anti-CD79 monoclonal antibodies, bispecific antibodies, chimeric antigen receptor-T therapy or hematopoietic stem cell transplantation. For other patients with resolved HBV infection, pre-emptive antiviral therapy guided by serial monitoring of HBV DNA is a reasonable option.

INTRODUCTION

Patients with chronic or resolved hepatitis B virus (HBV) infection are at risk of viral reactivation during chemotherapy or immunosuppressive therapy, commonly in patients receiving anti-cancer therapy for hematological malignancies or hematopoietic stem cell transplantation (HSCT). The earliest reports of HBV reactivation were in patients with lymphoma[1], and the highest risk of HBV reactivation is in patients receiving the potent anti-CD20 monoclonal antibodies such as rituximab or obinutuzumab, which result in profound B-cell depletion.

There have been major advances in the development of new targeted therapy in the treatment of hematological malignancies in the past two decades. Bruton tyrosine kinase (BTK) inhibitors are increasingly used in chronic lymphocytic leukemia (CLL) and lymphoma. Because these agents block B-cell antigen receptor signaling and thus

reduce malignant B-cell proliferation, BTK inhibitors may potentially reactivate HBV. Other examples include bispecific antibodies in the treatment of non-Hodgkin lymphoma (NHL), CD79b-targeted antibody-drug conjugate, *i.e.,* polatuzumab vedotin, for diffuse large B cell lymphoma (DLBCL) and anti-CD38 monoclonal antibodies used in multiple myeloma (MM) patients.

Chimeric antigen receptor (CAR)-T cell therapy is a promising intervention which can be applied to lymphoid malignancies and plasma cell diseases including acute lymphoblastic leukemia (ALL), NHL and MM. There is prolonged B-cell aplasia after CAR-T therapy which may potentially cause fatal HBV reactivation[2]. Hence, an understanding of the risk of HBV reactivation during treatment with novel therapies is important to prevent a fatal outcome.

This article will review the current published data on the clinical course and risk factors for HBV reactivation when using these novel therapies in patients with hematological malignancies. The recommended choice and duration of antiviral prophylaxis together with monitoring after stopping antiviral prophylaxis will also be discussed.

DEFINITIONS OF HBV REACTIVATION AND CLINICAL MANIFESTATIONS

Antibody to hepatitis B core (anti-HBc) is a good marker of current and past HBV infection as it persists even after hepatitis B surface antigen (HBsAg) is no longer detectable, while anti-HBs can be present due to successful hepatitis B vaccination or previous infection.

HBV reactivation is defined as exacerbation of chronic hepatitis B (CHB) or reactivation of past resolved hepatitis B infection. In general, reactivation is characterized by an increase from baseline in the HBV DNA level in patients with CHB, but it can also be defined as reverse HBsAg seroconversion, or the appearance of HBV DNA in serum when there is absence of HBsAg. The definition of HBV reactivation varies among different international guidelines and the information is summarized in Supplementary Table 1[3-7]. Hepatitis flare is defined as a 3-fold or more rise in alanine

aminotransferase (ALT) level compared with baseline and ALT level more than 100 U/L[7].

When a patient has been infected with HBV, the virus enters the hepatocytes where the viral genome is released and transported into the nucleus. Once inside the nucleus, the viral genome is then converted into plasmid-like covalently closed circular DNA (cccDNA), which can persist in the hepatocytes in a latent and stable state[8].

HBV reactivation may occur at any time during or after chemotherapy. There are five stages in the course of HBV reactivation[9]. The first stage includes an asymptomatic elevation in markers of viral replication, with detectable HBV DNA levels patients who are HBsAg-positive or -negative, or the reappearance of HBsAg in previously HBsAg-negative patients. In the second phase, serum HBV DNA levels continue to raise, and serum ALT and aspartate aminotransferase (AST) concentrations start increasing within a few weeks or days. This stage is also regarded as hepatic flare or HBV reactivation-related hepatitis. Most patients remain asymptomatic but a small number may experience constitutional symptoms, jaundice and right upper-quadrant pain. Patients may then enter a spontaneous or on-treatment improvement, *i.e.,* the third stage, in which the ALT and AST levels improve spontaneously or after administration of antiviral therapy. A small proportion of patients experience the fourth stage if the hepatic injury cannot be resolved, characterized by a decrease in hepatic synthetic function, deranged clotting profile and a rise of serum bilirubin levels. Fortunately, the majority of patients will go into the fifth stage with resolution of HBV reactivation after cessation of immunosuppressive therapy and the initiation of antiviral therapy. However, some may remain in stage 4, warranting liver transplantation in some severe cases.

In patients receiving immunosuppressive therapy, the loss of immune control may result in viral replication inside the hepatocytes without any increase in ALT levels. Nevertheless, upon immune reconstitution, sometimes during immunosuppressant tapering or withdrawal, the immune system will target the hepatocytes to clear the virus, resulting in liver damage[10].

RISK FACTORS FOR HEPATITIS B REACTIVATION

Host factors

Male sex and older age were identified to be risk factors for HBV reactivation[11-13]. A study in 626 HBsAg-positive patients who were undergoing chemotherapy for a variety of malignancies showed that there was almost a 3-fold increase of the incidence of HBV reactivation in men but the exact mechanism was not clear[13]. Chen *et al*[14] analyzed the risk of HBV reactivation among 1962 patients with hematological malignancy in Taiwan. The presence of hepatocellular carcinoma (HCC) and absence of antiviral prophylaxis were independent risk factors for HBV reactivation in HBV carriers. Among patients who were HBsAg negative at diagnosis, liver cirrhosis, diabetes mellitus, allogeneic stem cell transplantation and low anti-HBs titers were independent risk factors for HBV reactivation[14]. Lymphoma is also associated with higher risk of HBV reactivation[15]. Both the underlying disease and the anti-cancer therapy may contribute to HBV reactivation, indicating that the immunocompromised state is an important risk factor.

Virologic factors

The identified virologic risk factors for HBV reactivation include the presence of intrahepatic cccDNA and detectable HBV DNA levels[16-18]. Signs of increased viral replication, such as HBsAg or hepatitis B e antigen (HBeAg) positivity and detectable baseline HBV DNA, before treatment, are predictive of the patient meeting the criteria for HBV reactivation during treatment with cytotoxic chemotherapy or autologous stem cell transplantation[19-22].

HBV genotype is also related to treatment response, disease severity and progression[7,9]. For example, it was found that HBV genotype B is associated with HBeAg seroconversion at an earlier age, less active hepatic necroinflammation, more prolonged remission after HBeAg seroconversion, a slower rate of cirrhotic progression, and a reduced rate of HCC development compared with genotype C[7].

Salpini *et al*[23] identified mutations in HBsAg as being risk factors for reactivation. Using population-based and ultradeep sequencing, they analyzed the genetic diversity of HBsAg in 29 patients and found that 75.9% of HBV-reactivated patients carried mutations localized in immune-active HBsAg regions compared with only 3.1% of control patients ($P < 0.001$)[23]. The majority of these mutations resided in the B-cell epitopes of the HBs antigenic loop. Some of the mutations are known to hamper HBsAg recognition by humoral response, which may explain the frequent reactivation of HBV in patients receiving immunosuppressive therapy targeting B cells.

Types of anticancer therapies

Chemotherapy: Anthracycline chemotherapy (*e.g.,* doxorubicin, daunorubicin and idarubicin) is a common form of treatment for hematological cancers such as lymphoma and acute myeloid leukemia (AML). The risk of HBV reactivation is significant in patients receiving doxorubicin as part of the chemotherapeutic regimen[6].

Chen *et al*[24] found that there was increase in p21 expression during treatment with doxorubicin. The increase in p21 expression will promote the expression of CCAAT/enhancer-binding protein α (C/EBPα), which helps to activate HBV replication by enhancing the binding of C/EBPα to the HBV promoter. Kostyusheva *et al*[25] studied the effects of DNA-damaging compounds such as doxorubicin and hydrogen peroxide on the replication or reactivation of HBV and found that both doxorubicin and hydrogen peroxide dose-dependently activated HBV replication[25]. If doxorubicin is planned, anti-HBV prophylaxis is recommended for patients who are receiving doxorubicin if they have either CHB infection or a past resolved HBV infection.

Steroids: Steroids are commonly combined with chemotherapy or immunomodulatory drugs in the treatment of many hematological malignancies such as lymphoid malignancies and MM. Steroids can increase the HBV replication through two mechanisms. First, they can prevent T and B cell proliferation by suppressing cell-

mediated immunity through the inhibition of interleukins[26]. Second, they exert a direct suppressive effect on T cell-mediated immunity through the stimulation of the glucocorticoid-responsive element present in the HBV genome[27].

Cheng *et al*[28] randomized 50 lymphoma patients who were HBsAg-positive and receiving the same chemotherapeutic regimen to treatment with or without the addition of corticosteroids, and compared the rate of HBV reactivation. The cumulative incidence of HBV reactivation was significantly higher in the corticosteroid group at 9 mo (73% *vs* 38%, respectively, *P* = 0.03). In a separate prospective cohort study with 6 years of follow-up, HBV reactivation occurred at 4 to 32 mo (median 10 mo) after the administration of steroids[29]. Most patients had malignancies or rheumatologic diseases.

The risk of HBV reactivation is further increased in patients who receive high-dose steroids (> 20 mg/d of prednisolone) and/or a long duration of therapy (> 4 wk)[6]. In a recent prospective study of 1303 patients with rheumatic diseases and past resolved HBV infection, it was found that patients taking steroids at a time-weighted average dose of higher than 20 mg/d prednisone-equivalents are at high risk for HBV reactivation or even hepatitis flare[30]. Prophylactic anti-HBV therapy should be considered for these high-risk patients.

Tyrosine kinase inhibitors: Currently, treatment with tyrosine kinase inhibitors (TKIs), *e.g.,* imatinib, nilotinib, dasatinib and ponatinib, is standard therapy for chronic myeloid leukemia (CML). The exact mechanism for HBV reactivation with TKIs is not known but it may be related to immune restoration. There are some published data on the risk of HBV reactivation in patients receiving TKIs. One hundred forty-two Taiwanese adult CML patients were enrolled in a study to assess the rate of HBV reactivation during TKI therapy, including imatinib (*n* = 43, 30.3%), dasatinib (*n* = 48, 33.8%), nilotinib (*n* = 37, 26.1%) and ponatinib (*n* = 1, 0.7%), two or more TKIs (*n* = 13, 9.2%)[31]. Nineteen patients were HBV carriers and the rate of HBV reactivation was 26.3%; HBV reactivation was detected between 3 and 51 mo after the use of TKIs. Three patients experienced HBV-

related hepatitis with an increase in ALT of more than 100 U/L[29]. One of the patients with HBV reactivation had received antiviral prophylaxis with entecavir; he was then given tenofovir after HBV reactivation.

A Korean study involved 69 patients with CHB infection being assessed for HBV reactivation[30]. Forty-six patients did not receive antiviral prophylaxis and the rate of HBV reactivation was 26% in this group of patients[32]. HBV reactivation was detected in seven patients who received imatinib, two patients receiving dasatinib, one nilotinib recipient, and one patient treated with radotinib therapy.

We would recommend prophylactic antiviral therapy to HBV carriers, and monitor HBV DNA and liver enzymes every 1 to 3 mo in patients with past resolved HBV infection, during TKI treatment. If the HBV DNA level rises, pre-emptive treatment with antiviral agent should be given. TKIs may also be used in combination with chemotherapy in the treatment of Philadelphia-positive ALL[33,34]. The combination with chemotherapy will likely lead to a deeper immunosuppressive effect, so prophylactic antiviral therapy is recommended in any patient with either CHB infection or past resolved HBV infection.

Anti-CD20 monoclonal antibodies: Treatment for a number of different hematological malignancies, including CLL and B-cell lymphoma, often includes B cell-depleting agents such as anti-CD20 monoclonal antibodies. Rituximab, obinutuzumab, and ofatumumab target the CD20 B-lymphocyte antigen and lead to marked depletion of the B cells involved in priming specific cytotoxic T cells[35]. Rituximab also worsens the impairment of antigen-presenting B cells which is seen in patients with CHB, resulting in inadequate induction of CD4 T cell activation and proliferation, and a T cell hyporesponsive state[36]. There is more than a 5-fold increase in the risk of HBV reactivation associated with the use of rituximab[37].

Both HBsAg-positive patients and those with resolved HBV infection are susceptible to HBV reactivation when they receive rituximab[38-41]. The incidence varies from 8.3%

to 25% in patients with resolved HBV infection receiving rituximab-based chemotherapy[42-46]. Rituximab is a significant risk factor for HBV reactivation.

Obinutuzumab is a second-generation anti-CD20 monoclonal antibody. It has an engineered fragment crystallizable portion and a modified elbow hinge region[47]. Obinutuzumab has shown better efficacy than rituximab in several types of lymphoid diseases, by inducing direct cell death and enhancing antibody-dependent cellular cytotoxicity[48,49]. It can potentially cause more profound suppression of CD20 than rituximab[48,49]. It is used in patients with CLL and follicular lymphoma with promising results[48,49].

Kusumoto et al[50] performed a prospective study in 326 B-cell lymphoma patients with past resolved HBV infection who received obinutuzumab- (n = 155) or rituximab- (n = 171) containing immunochemotherapy in the phase 3 GALLIUM[48] and GOYA[51] studies. Of the 326 patients with resolved HBV infection, 119 (36.5%) received nucleos(t)ide analog treatment (NAT). Among these 119 patients, 94 received prophylactic NAT and 25 received pre-emptive NAT. The rate of HBV reactivation was 10.8% without antiviral prophylaxis, whereas only two of the 94 patients who received prophylactic NAT (2.1%) had HBV reactivation[48]. It was shown that the baseline detectable HBV DNA was strongly associated with an increased risk of reactivation while prophylactic NAT significantly decreased the risk on multivariate Cox analysis[50].

The reactivation rate in patients receiving obinutuzumab- and rituximab-based chemotherapy was 13.2% and 6.1%, respectively[50]. Although no significant difference in the risk of HBV reactivation between these two different immunochemotherapy regimens was demonstrated in the multivariate analysis, it might be due to confounding factors including imbalance of baseline risk factors. Anti-HBV prophylaxis is recommended in patients with either CHB infection or past resolved infection receiving anti-CD 20 monoclonal antibody.

Monoclonal antibodies other than anti-CD 20

Polatuzumab vedotin: Polatuzumab vedotin is an antibody-drug conjugate targeting CD79b, which is universally expressed on the surface of malignant B cells. CD79b is a signaling component of the B-cell receptor which is located on the surface of normal B cells as well as most of the mature B-cell tumors and 95% of DLBCL[52]. Polatuzumab vedotin was found to be useful in combination with bendamustine and rituximab (pola-BR) for patients with relapsed or refractory DLBCL[53]. It can also be used in a modified regimen of polatuzumab vedotin, rituximab-cyclophosphamide, doxorubicin, and prednisolone (pola-R-CHP) with success in the frontline treatment of DLBCL[54]. The risk of disease progression, relapse, and death were all reduced among those who received pola-R-CHP than among those who received standard rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy in previously untreated DLBCL patients with intermediate-risk or high-risk.

To date, there are no published data or reported cases of HBV reactivation in patients receiving polatuzumab vedotin. In view of the profound B-cell suppression that occurs when these regimens are used to treat lymphoma, we would recommend antiviral prophylaxis for patients receiving polatuzumab vedotin if they have either CHB infection or past resolved HBV infection.

Inotuzumab ozogamicin: Inotuzumab ozogamicin is an antibody conjugate in which a humanized monoclonal antibody against CD22 is conjugated to the cytotoxic antibiotic calicheamicin[55]. After binding to CD22 on the leukemic cell surface, the CD22-conjugate complex is rapidly internalized, releasing the calicheamicin. Once released, the cytotoxic portion of the conjugate binds to the minor groove of DNA in these leukemic cells, and induces double-strand cleavage and subsequent apoptosis.

More than 90% of patients with B-cell ALL express CD22 and this cell-surface glycoprotein is not shed into the extracellular matrix, making it a logical target for B-cell cancer therapy[56]. It has been used with success in the treatment of ALL and it can deplete B cells. There have been no reports to date of HBV reactivation in patients with CHB infection or past resolved infection receiving inotuzumab ozogamicin. However,

in view of the profound B-cell depletion, we would recommend antiviral prophylaxis during inotuzumab ozogamicin in patients with either CHB infection or past resolved infection.

Blinatumomab: Blinatumomab is a bispecific T-cell engager, with two binding sites: One for CD3-positive cytotoxic T cells and one for CD19-positive B cells. By drawing the two types of immune cells together, blinatumomab facilitates the recognition and destruction of CD19-positive ALL blasts by the patient's own endogenous T cells[57]. It has been used with success in the treatment of relapsed/refractory ALL or as consolidation therapy[58,59].

We did not identify any published cases of HBV reactivation in patients with CHB infection or past resolved infection receiving blinatumomab. HBV prophylaxis is recommended for both chronic and resolved HBV infection in patients receiving blinatumomab, in view of profound B-cell depletion seen with this agent.

Daratumumab and isatuximab: Daratumumab is a human immunoglobulin G1 monoclonal antibody which targets CD38-expressing cells. Several of the combination regimens containing daratumumab have shown promising results in the treatment of newly diagnosed and refractory/relapsed MM[60-63]. It also has an emerging role in the treatment of amyloid light-chain amyloidosis[64,65].

The principal mechanism of daratumumab in MM is to induce death of CD38-expressing myeloma cells *via* antibody-dependent and complement-dependent cytotoxicity, as well as *via* antibody-dependent cellular phagocytosis[66]. Daratumumab also targets normal plasma cells expressing CD38, leading to a reduction in the humoral immunity against reactivation of HBV[67].

There was a report of HBV reactivation occurring on day 15 of the third course of a daratumumab-containing regimen in a MM patient with resolved HBV infection[68]. Lee *et al*[69] also conducted a retrospective study of 93 patients with resolved HBV infection who had been treated with daratumumab and found that the risk of HBV reactivation

was 6.5% at a median follow-up period of 8.7 mo. One patient later died of hepatic failure despite treatment with tenofovir. These reports highlight the risk of reactivation of resolved HBV infection after daratumumab treatment in MM patients.

Isatuximab, another anti-CD38 monoclonal antibody, has demonstrated benefits in the treatment of patients with relapsed/refractory and high-risk MM[70-73]. We would recommend anti-HBV prophylaxis in both HBV carriers or those with resolved HBV infection during treatment with either daratumumab or isatuximab in view of the similar mechanisms of action of both drugs.

Novel therapies for hematological malignances
CAR-T cell therapy: CAR-T cell therapy is a promising immunotherapy with curative intent for several types of hematological malignances including NHL[74-77], ALL[78], and MM[79,80]. CAR-T cell therapy involves removal of the patient's own T cells, reprogramming these cells with a CAR construct and then returning them to the patient's bloodstream, where these programmed T cells attack the cancer cells[81]. The activated CAR-T cells identify targets on cancer cells specifically leading to the destruction of these cancer cells. Because is easier to target an adequate tumor antigen in hematological malignances (such as CD19 in lymphoid malignances) than it is in solid cancers, CAR-T cell therapy has been first applied to hematological malignances.

The issue of HBV reactivation in patients receiving CAR-T cell therapy remains unexplored, and the data on HBV reactivation in these patients are limited. CAR-T cells may predispose HBV immune patients to reactivation due to its cytotoxicity against B cells. The proper prevention strategy and duration of antiviral prophylaxis in patients receiving CAR-T cell therapy are still unclear and should be further investigated. There has been a fatal case of HBV reactivation after CAR-T therapy[2]. HBV reactivation can be a significant complication in CAR-T cell treatment and clinicians should be cautious about this complication particularly in areas where HBV is still prevalent.

Patients can also have late HBV reactivation occurring more than 1 year after CAR-T cell therapy. CAR-T cells can persist in the blood for a long time, resulting in prolonged

B-cell aplasia and a persistent reduction in immunoglobulin production thus contributing to late reactivation[82].

Table 1 summarizes the published data on the HBV reactivation in patients receiving CAR-T therapy[83-89]. The rate of HBV reactivation ranged from 0% to 20% for CHB[83-89]. We recommend that clinicians administer anti-HBV prophylaxis during the CAR-T therapy and for at least 1 year afterwards in patients who had CHB or past resolved HBV infection[82].

Bispecific antibodies: The development of bispecific antibodies has been an important advance in the treatment of relapsed or refractory B-cell lymphomas[90-92], including DLBCL[93-95] and follicular lymphoma[96]. Bispecific antibodies target both T cells and CD19 or CD20 on malignant B cells and is a promising immunotherapy in the treatment of NHL. These dual binding sites draw malignant B cells close to endogenous T cells, thereby directly activating T-cell cytotoxicity. Examples of the bispecific antibodies include glofitamab, mosunetuzumab, epcoritamab and odronextamab. Some of these bispecific antibodies have a fixed duration of therapy and some, such as epcoritamab, are administered until disease progression.

Since there are a lack of prospective or retrospective studies on the risk of HBV reactivation in patients receiving bispecific antibodies, the real incidence of HBV reactivation is unclear. However, bispecific antibodies will profoundly suppress B-cell activity. These drugs are highly potent and the effect on B-cell depletion is expected to be significant. Therefore, we recommend antiviral prophylaxis against HBV in patients with either CHB infection and past resolved HBV infection.

BTK inhibitors: BTK inhibitors such as ibrutinib, acalabrutinib and zanubrutinib have shown success in the treatment of many lymphoid malignancies including CLL[97-102], mantle cell lymphoma[103,104], marginal zone B-cell lymphoma[105], and Waldenström's macroglobulinemia[106]. Ibrutinib blocks B-cell antigen receptor signaling, thus reducing malignant proliferation of B cells and inducing cell death[107].

The effect of ibrutinib or other BTK inhibitors on HBV reactivation has not been extensively studied, and there are no guidelines on the prophylaxis and management of HBV reactivation during treatment with ibrutinib. Table 2 summarizes the current data on the risk of HBV reactivation and their outcomes in patients receiving BTK inhibitors[108-111]. Most existing data are from retrospective studies. The rate of HBV reactivation ranged from 1.9% to 8.3% for past resolved infection. BTK inhibitors will induce profound B-cell suppression. Hence, we recommend anti-HBV prophylactic treatment with nucleotide analogues for lymphoma patients with positive HBsAg or resolved HBV infection with detectable HBV DNA who are receiving BTK inhibitors. For those with resolved HBV infection and negative HBV DNA, we recommend monitoring HBV DNA levels and liver function every 1 to 3 mo, and giving pre-emptive antivirals when the HBV DNA level rises.

B cell lymphoma-2 inhibitors: The B cell lymphoma (BCL)-2 inhibitor venetoclax is commonly used in the treatment of CLL[112,113] and in combination with azacitidine or low-dose cytarabine in AML patients who are not fit for intensive chemotherapy[114,115]. Venetoclax is a potent inhibitor of the antiapoptotic BCL-2 protein. AML stem cells express BCL-2 and depend on BCL-2 for survival. Venetoclax has synergistic effects when used in combination with azacitidine.

There is a lack of large retrospective or prospective studies on the incidence of HBV reactivation in patients receiving venetoclax, so the risk is unclear. Because of its mechanism of action, venetoclax will profoundly suppress B-cell activity. Thus, the same prophylactic or pre-emptive antiviral management approach used for patients receiving BTK inhibitors should be applied in patients receiving venetoclax.

Proteasome inhibitors: The proteasome inhibitors have become the backbone treatment of MM. They include bortezomib, carfilzomib and ixazomib. Bortezomib is the most commonly used proteasome inhibitor. Bortezomib can target cellular pathways essential for the proliferation of malignant plasma cells. However, it may also

negatively impact the functions of healthy B cells and plasma cells, which are important in the immune control of HBV. It can also dysregulate cell-mediated immunity and may increase HBV reactivation by affecting the number and functions of CD8 T cells and CD56 natural killer cells[116].

Ataca Atilla et al[117] conducted a retrospective study in 178 MM patients who had received lenalidomide and/or bortezomib. They found that the rate of HBV reactivation was 3% after bortezomib and 8% after bortezomib and lenalidomide[117]. Lee et al[118] reported HBV reactivation in 5.2% of 230 MM patients with past resolved HBV infection after a median follow-up of 2.4 years. 134 patients (58%) had received bortezomib-based therapy. In this study, the cumulative rate of HBV reactivation was 5% at 2 years and 8% at 5 years[118].

Mya et al[116] reported an HBV reactivation incidence of 5.5% in 273 relapsed or refractory MM patients who had received bortezomib and dexamethasone therapy. Li et al[119] conducted a retrospective study of HBV reactivation in patients receiving regimens containing bortezomib. Twenty-seven of the 139 patients were HBsAg positive and 22 of them were given antiviral prophylaxis with lamivudine or entecavir. HBV reactivation occurred in six HBsAg-positive and two HBsAg-negative/anti-HBc positive cases from a total of 139 patients[119]. Antiviral prophylaxis is recommended for both CHB patients and those with past resolved HBV infection who are receiving proteasome inhibitors.

Immune checkpoint inhibitors: Immune checkpoint inhibitors (ICI) are effective in the treatment of solid tumors, and have also shown efficacy in the treatment of lymphoma[120-124]. The ICIs can block the localization and traffic of activated lymphocytes, thus inhibiting the inflammatory response associated with immune-mediated diseases[125]. The ICIs may also reduce the local immune control of HBV replication in the liver, predisposing patients to HBV reactivation.

Table 3 summarizes the data on HBV reactivation in patients receiving ICIs[126-129]. The rate of HBV reactivation among HBsAg-positive cancer patients is 0.5% to 5.3%

during ICI therapy. Prophylactic antiviral treatment is recommended for HBsAg-positive patients to prevent HBV reactivation. For those with resolved HBV infection patients and undetectable HBV DNA levels, we recommend monitoring liver function and HBV DNA levels every 1 to 3 mo, and administering pre-emptive treatment with antiviral agents if an increase in HBV DNA levels is detected.

PREVENTION OF HEPATITIS B REACTIVATION

Existing guidelines on the drug classes and the corresponding risk of HBV reactivation are summarized in Table 4, while Table 5 summarizes the international guidelines on the management of patients with HBV infection receiving chemotherapy. The recommendations for management of HBV-infected cancer patients receiving novel agents for hematological malignancies are shown in Table 6.

Screening for hepatitis B

In order to prevent HBV reactivation among patients with hematological malignancies, it is essential to identify those with HBV infection before starting chemotherapy or immunotherapy. This starts with screening for the presence of HBsAg and anti-HBc in blood. The commercial immunoassays usually capture HbsAg having specificity for epitopes present on the antigenic α determinant. The enzyme-linked immunosorbent assay method used in HBsAg detection has around 80% of sensitivity and specificity, compared with more than 90% using the immunochromatographic test[130]. Complete loss of anti-HBc with chronic and high viremic HBV infection after allogeneic stem cell transplantation has been reported[131]. However, there might be some rare scenarios where HBsAg or anti-HBc are falsely negative. For example, mutations within the α determinant may affect the conformation of the surface epitope such that it is unrecognizable to the test, or mutations in other parts of the viral genome may affect HbsAg secretion or expression, resulting in diagnostic escape[132]. Moreover, there has been a case report describing complete loss of anti-HBc after allogeneic stem cell transplantation in a patient with resolved HBV infection who previously had positive

anti-HBs and anti-HBc prior to the stem cell transplant[131]. Isolated anti-HBs without anti-HBc may be present in pretreated patients without previous hepatitis B vaccination[133,134]. Thus, a more sensitive combined screening strategy is advisable, including serological testing for HBsAg, anti-HBc, anti-HBs and a sensitive test for HBV DNA.

HBsAg-positive patients without hepatitis at baseline

A preventive strategy is more effective than a pre-emptive strategy in HBsAg-positive patients[135,136]. We recommend giving NAT for prophylaxis in all HBsAg-positive candidates prior to immunosuppressive therapy irrespective of their HBV DNA because the risk of HBV reactivation is high in this group of patients. This approach is highly effective, with a number needed to treat to prevent one episode of HBV reactivation of three[135].

It is not always possible to prevent the development of hepatitis or hepatitis flares if antiviral therapy is started after the onset of HBV reactivation[42], since it will take some weeks or even months for the antiviral therapy to reduce viral loads, and the inflammation and necrosis of the liver will be ongoing during this period[137].

HBsAg-negative and anti-HBc-positive patients

The risk of HBV reactivation in this group varies considerably, depending on the level of viremia and the immunosuppressive regimens administered. In general, if HBV DNA is detectable, the patient would be given anti-HBV prophylaxis and treated similarly to HBsAg-positive patients. If HBV DNA is undetectable, then the risk of reactivation associated with the immunosuppressive regimen will be assessed. High-risk groups such as those receiving anti-CD20 monoclonal antibodies should receive antiviral prophylaxis with NAT. Pre-emptive treatment is recommended for moderate- and low-risk groups, with HBV DNA monitoring every 1-3 mo.

Huang *et al*[43] compared pre-emptive with prophylactic entecavir therapy during R-CHOP chemotherapy in patients with lymphoma and resolved hepatitis B. Prophylactic

entecavir treatment significantly reduced the risk of HBV reactivation compared with pre-emptive antiviral therapy (17.9% *vs* 2.4%, *P* = 0.027)[43]. Therefore, the prophylactic strategy is a better option in patients receiving high-risk immunosuppressive regimens (Table 5).

HBsAg-negative/ anti-HBc-negative/ anti-HBs-negative patients

HBV vaccination can be considered in patients who are HBsAg-negative, anti-HBc negative and anti-HBs negative[3]. Anti-HBs potentially provide a protective effect against HBV reactivation[45,138-141]. The results of a meta-analysis showed that, among patients not receiving antiviral prophylaxis, the reactivation risk was 14% in the 388 patients who had anti-HBc only *vs* 5.0% in 1284 patients with concomitant anti-HBs. The pooled odds ratio of HBV reactivation was 0.21 (95% confidence interval: 0.14-0.32) in those with anti-HBs compared with anti-HBc only[141].

HBsAg negative/anti-HBc negative/anti-HBs positive patients

It is rare to have HBV reactivation in patients with isolated anti-HBs, but there have been occasional reports of HBV reactivation in patients with only anti-HBs seropositivity[133,134]. In one report, a patient with follicular lymphoma, who had not been vaccinated for hepatitis B, was positive for anti-HBs but negative for anti-HBc prior to starting chemotherapy. He subsequently developed high HBV DNA levels (1.8 × 10^8 copies/mL), and was found to have an HBV escape mutant, which was difficult to detect using the standard HBsAg assays[133]. HBV escape mutants harbor mutations in the essential antigenic area of HBsAg, and are capable of growing in the presence of anti-HBs. In these circumstances, anti-HBc may appear very late.

In a separate report, a patient with DLBCL (also without a record of hepatitis B vaccination) had a pre-chemotherapy HBV profile that was positive for anti-HBs (127 IU/mL) but negative for HBsAg and anti-HBc. She developed HBV reactivation after completing rituximab-based chemotherapy. Antiviral treatment with entecavir was started after HBV reactivation was detected. Despite that, she had clinical deterioration

with development of hepatic encephalopathy and died of liver failure finally[134]. Figure 1 shows a suggested algorithm for HBV testing and management of patients with hematological malignancies receiving anticancer therapy.

CHOICE OF ANTIVIRAL THERAPY

For the treatment of chronic HBV infection, entecavir or tenofovir are the preferred antiviral agents because they have high genetic barriers to resistance compared with lamivudine. Huang *et al*[142] performed a prospective randomized study in 121 HBsAg-positive patients with untreated DLBCL. Sixty patients received lamivudine prophylaxis and 61 received entecavir prophylaxis. Various endpoints occurred at a significantly lower rate in the entecavir than the lamivudine group, including HBV reactivation (6.6% *vs* 30%, P = 0.001), HBV-related hepatitis (0% *vs* 13.3%, P = 0.003), and chemotherapy disruption (1.6% *vs* 18.3%, P = 0.002)[142].

A meta-analysis of 770 patients with lymphoma showed that, in patients with CHB, the risk of HBV reactivation was significantly higher in those receiving prophylactic lamivudine compared with entecavir (P < 0.001)[143]. The superior prophylactic efficacy of entecavir is supported by studies in allogenic HSCT recipients and solid tumor patients, which showed a lower rate of HBV reactivation with entecavir compared with lamivudine[20,144]. Meta-analyses have also shown that tenofovir and entecavir are the most effective antiviral agents for the prevention of HBV reactivation[145,146]. Entecavir treatment of HBV patients with lamivudine-resistant viral strains is usually unsuccessful due to the rapid selection of additional mutants[147], highlighting the importance in choosing an effective initial anti-viral therapy.

Duration of antiviral therapy

Most guidelines recommend continuing antiviral therapy for 1 year after the cessation of anti-cancer therapy, and some guidelines recommend extending antiviral treatment for up to 18 mo after the last dose of cancer therapy (Table 6)[3,4,148]. Delayed HBV reactivation has been reported in patients who received anti-CD20 antibody therapy

such as rituximab since rituximab will delay the immune recovery[149,150]. HBV DNA levels should be checked before stopping antiviral treatment.

Monitoring after stopping antiviral prophylaxis

HBV reactivation can develop after cessation of NAT[149,151,152], so monitoring for HBV reactivation is recommended after stopping anti-HBV prophylaxis (Table 6). In general, liver function tests and HBV DNA are monitored every 3 mo for a minimum of 12 mo after discontinuation of antiviral agents[3,4,7]. Monitoring for more than 12 mo is recommended for patients who received anti-CD20 monoclonal antibody therapy.

Management of HBV reactivation

Prophylaxis is better than treatment because fatal outcomes may still occur in patients with HBV reactivation even with antiviral treatment[153]. Foont and Schiff[154] performed a systematic review on the use of lamivudine for the prophylaxis of HBV reactivation in patients on chemotherapy. In the 10 trials with 173 patients included in the analysis, two patients taking lamivudine prophylaxis developed fatal HBV reactivation[154]. If a patient is not on antiviral prophylaxis, treatment with an antiviral agent such as entecavir or tenofovir should be initiated. Hepatitis B flare-ups are generally uncommon in patients receiving anti-HBV prophylaxis with potent antiviral agents, but drug resistance can develop to prophylactic lamivudine. In this instance, salvage therapy such as entecavir or tenofovir may be beneficial to them. Some patients achieve biochemical and virological recovery after combination treatment with entecavir + adefovir or lamivudine + adefovir[155].

The purpose of the treatment is prevention of severe hepatitis and also hepatic failure, which are potentially fatal. It is important to closely monitor the patient's liver enzymes, clotting profile and bilirubin levels. Patients can still progress to hepatic failure despite therapy with nucleoside analogs[42], especially when there is already a marked increase in liver enzymes or jaundice. Liver transplantation is an option for patients with liver failure and there have been reported cases of successful

transplantation in patients with chemotherapy-induced HBV reactivation[156-160]. Benten *et al*[161] found a low recurrence of pre-existing extrahepatic malignancies after liver transplantation.

CONCLUSION

Many novel therapies have emerged for the treatment of hematological malignancies in the past two decades and the results are promising. The issue of prevention of HBV reactivation is an important part of the management. Hepatitis due to HBV reactivation is a potentially fatal complication of cancer chemotherapy in patients with hematological malignancies. HBV reactivation can be prevented through blood test screening and, in patients with moderate or high risk of HBV reactivation, prophylactic antiviral therapy. We recommend screening all hematology patients for HBsAg and anti-HBc prior to receipt of anticancer therapy, and risk stratification based on the types of therapies planned and the serologic status of the patients. Prophylactic antiviral therapy is important for HBsAg-positive patients. Two options are available for HBsAg-negative/anti-HBc-positive patients. One is routine prophylactic antiviral therapy. The other is serial HBV DNA monitoring, and pre-emptive antiviral drug administration as soon as HBV DNA is detected. While there is still limited evidence on the risk of HBV reactivation with newer therapies, we recommend antiviral prophylaxis in patients with resolved HBV who are scheduled to receive high-risk therapies like anti-CD20 monoclonal antibodies, anti-CD79 monoclonal antibody, bispecific antibodies, BTK inhibitors, BCL-2 inhibitors, CAR-T therapy or HSCT.

Entecavir or tenofovir are the preferred choices for prophylactic therapy. Preventative antiviral therapy should be continued for at least 12 mo after the cessation of chemotherapy; longer durations are recommended for patients who received rituximab or those who had high levels of serum HBV DNA before starting chemotherapy. Checking the HBV DNA before the cessation of antiviral therapy is recommended. We would also recommend monitoring liver function and HBV DNA levels for at least 12 mo after the cessation of antiviral prophylaxis.

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