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TOPIC HIGHLIGHT

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Chemotherapy-related reactivation of hepatitis B infection: Updates in 2013

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Abstract

Hepatitis B reactivation is a potentially serious complication of anticancer chemotherapy, which occurs during and after therapy. This condition affects primarily hepatitis B surface antigen (HBsAg)-positive patients, but sometimes HBsAg-negative patients can be at risk, based only on evidence of past infection or occult infection with a low titer of detectable hepatitis B virus (HBV) DNA. The clinical outcomes vary with the different degrees of virologic and biochemical rebound, ranging from asymptomatic elevations in liver enzymes to hepatic failure and even death. Despite the remarkable advancement in the treatment of chronic hepatitis B over the past decade, proper strategies for the prevention and management of HBV reactivation remain elusive. Moreover, with the increasing use of rituximab in patients with lymphoma, HBV reactivation in occult or past infections has become increasingly problematic, especially in HBV-endemic regions. This review addresses the current knowledge on the clinical aspects and management of chemotherapy-related HBV reactivation, updates from recent reports, several unresolved issues and future perspectives.

Key words: Hepatitis B virus; Chemotherapy; Reactivation

Core tip: Hepatitis B reactivation is a serious complication of anticancer chemotherapy, affecting both hepatitis B surface antigen-positive and anti-hepatitis B core antibody-positive patients. Although treatment of hepatitis B has been dramatically improved in the past decade, management of hepatitis B virus (HBV) reactivation remains unsatisfactory. This review covers updates from recent reports, unresolved issues and future perspectives on HBV reactivation.

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INTRODUCTION

Overview

Chronic infection with hepatitis B virus (HBV) is a major health burden that affects approximately 350 million people worldwide[1]. The hallmark of progressive liver disease in HBV infection is active viral replication. In contrast, patients with low serum HBV DNA level (usually below 1000 IU/mL) and normal alanine aminotransferase (ALT) activity are considered inactive carriers with a low risk of clinical progression. However, HBV reactivation can occur in these inactive carriers, either spontaneously or upon immunosuppression[2]. Impairment of the host immune system due to treatment with chemotherapeutic or immunosuppressive agents raises the risk of HBV re-

activation[3]. HBV reactivation presents with reemergence of necroinflammation in patients of inactive carrier status or even in patients with resolved hepatitis B[4], which is preceded by rise in serum HBV DNA of 10 times or higher, sometimes reaching $\geqslant 10^8$ IU/mL, with serum ALT elevation (≥ three times of upper limit of normal or an absolute rise of more than 100 IU/L)[5,6]. Prior to the diagnosis of HBV reactivation, it is necessary to exclude other conditions which might cause abovementioned biochemical changes, including hepatic injury due to chemotherapy, metastatic malignancies in the liver, or hepatitis due to other viruses. The reported rate of HBV reactivation was diverse among literature, approximately ranging from 20%-50%. Although initial presentation of HBV reactivation is mostly asymptomatic, some patients show clinical deterioration with the development of jaundice or other signs of decompensation, with some patients dying due to hepatic failure[5,7-9]. Typically, serum HBV DNA becomes detectable during anticancer therapy or immunosuppression, and then serum ALT rises after completion of the treatment. If HBV reactivation occurs in relation to chemotherapy among patients with malignancy, subsequent treatment disruption or premature termination may adversely influence treatment outcomes[10-12].

Risk factors

Several clinical predictors of HBV 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. HBV reactivation occurs more frequently in patients with non-Hodgkin's lymphoma with higher reported rates ranging from 24% to 67% compared to patients with solid tumors[8,13]. This finding is directly attributable to the intense chemotherapeutic regimens for lymphoma and relatively higher rates of hepatitis B surface antigen (HBsAg) positivity in lymphoma patients[8,13-15]. The risk of HBV reactivation is raised with corticosteroid use because of immune suppression or the direct stimulation of HBV replication. Rituximab, which commonly comprises chemotherapy regimens with corticosteroids for lymphoma, raises the risk of reactivation even further[16,17]. In hematopoietic stem cell transplantation for hematologic malignancies, preceding highly intensive chemotherapy frequently increases the risk of HBV reactivation[18,19]. Given the reactivation rate of 14%-21% in solid tumors, reactivation was more frequently reported in breast cancer (41%-56%), which might be explained by the higher doses of chemotherapy and the use of anthracycline[12,20,21]. Other known factors for the elevated risk of HBV reactivation are HBV genotype, specific mutations on HBV genome such as precore/core and precore promoter mutations, and recovery from neutropenia[22-25]. In addition to HBsAg-positive patients, HBV reactivation rarely occurs in anti-hepatitis B core immunoglobulin G (anti-HBc IgG)-positive patients without HBsAg; this result that can be interpreted as an occult HBV infection or a past infection[26]. In an occult or past HBV infection, HBV DNA can be detected in the hepatocytes or even in the serum with a low titer. If HBV reactivation occurs from the occult/past infection, HBV replication resumes following immunosuppression with or without the reemergence of HBsAg (reverse seroconversion or seroreversion of HBsAg)[5,27,28]. The risk of HBV reactivation in occult/past infection was particularly well documented in patients with rituximab-treated B-cell lymphoma or patients who underwent hematopoietic stem cell transplantation for their hematologic malignancies[29-35]. Low titer of hepatitis B surface antibody (HBsAb) was suggested as a risk factor of HBV reactivation in rituximab-treated lymphoma patients[17]. In addition, caution is needed in HBsAb-positive patients without HBsAg or anti-HBc IgG, since there have been case reports where HBV reactivation occurred in such patients causing fatality[36]. Risk factors for HBV reactivation are summarized in Table 1.

Management

In addition to its adverse influences on the maintenance of chemotherapy and on the outcomes of underlying malignancy, prevention of HBV reactivation is of paramount importance when considering the potential risk of hepatic failure or death. For prevention, the evidence of HBV infection (HBsAg and anti-HBc IgG) should be screened before the initiation of chemotherapy. HBV vaccination is indicated in case of negativity for both HBsAg and anti-HBc IgG. Preemptive antiviral therapy is needed for HBsAg-positive patients, irrespective of their serum HBV DNA levels[24]. Randomized controlled studies from Hong Kong and Taiwan demonstrated that preemptive lamivudine significantly reduced HBV reactivation, hepatic failure and mortality in lymphoma patients[14,19,37,38]. Based on those studies, current guidelines recommend starting preemptive antiviral therapy from the beginning of chemotherapy, rather than deferring until HBV DNA rises, and maintaining preemptive therapy for a specific period of time after the end of chemotherapy (*e.g.*, 6 mo or longer, up to 12 mo)[38-40]. However, the optimal duration of preemptive antiviral therapy remains elusive to date due to the lack of evidence. The risk of HBV reactivation was increased after the cessation of preemptive lamivudine therapy 3 mo following the end of chemotherapy, particularly in cases with high pre-chemotherapy HBV DNA (≥ 2000 IU/mL)[41]. Hence, the optimal duration for patients with high pretreatment HBV DNA can be determined according to the current treatment guidelines for chronic hepatitis B. In addition, it should be noted that HBV reactivation may occur following longer than 6 mo from the cessation of chemotherapy irrespective of the pretreatment viral load. Evidence on the proper choice of preemptive antiviral agents is also limited. However, antiviral agents other than lamivudine, such as adefovir, tenofovir, entecavir, and telbivudine, could be used for preemptive therapy, considering their similar mechanisms of action and advantages in potency

Table 1 Risk factors for anticancer chemotherapy-related hepatitis B virus reactivation

Categories	Risk factors	Ref.
Host factors	Male gender	[8]
	Young age	[8]
	Elevated baseline ALT	[63]
Tumor- or treatment-related factors	Lymphoma	[6,8]
	Hematologic malignancies	[8,64]
	Brease cancer	[6]
	Glucocorticoid use	[6,16]
	Anthracycline use	[6]
	Rituximab-based regimen	[17,29]
	Hematopoietic stem cell transplantation	[65]
Viral factors	High pre-chemotherapy viral load	[66]
	Positive HBeAg	[8,67]
	Presence of precore mutant	[25,68]
	Negative or low titer of HBsAb (in case of occult/past infection)	[17]

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBsAb: Hepatitis B surface antibody.

and resistance (especially for entecavir and tenofovir). Since resistance to lamivudine was reported even during the preemptive use, other antiviral agents with a high genetic barrier to resistance should be preferred in cases of prolonged chemotherapeutic schedules (*e.g.*, more than a year)[14]. Recently, a retrospective study demonstrated a reduced risk of hepatitis and chemotherapy disruption due to HBV reactivation with entecavir compared with lamivudine in lymphoma patients[42]. However, relevant data regarding the superior efficacy or cost-effectiveness of certain antiviral agents have remained scarce until the present. Without the consideration of cost, entecavir and tenofovir are relatively safer choices in view of their high potency and low resistance profiles. (Peg-)interferon is contraindicated as a preemptive antiviral agent because of its myelosuppression and possible exacerbation of hepatitis. Although patients with occult/past HBV infection (*i.e.*, anti-HBc IgG-positive and HBsAg-negative patients) possess a potential risk of reactivation, preemptive treatment cannot be uniformly recommended because their specific HBV reactivation risks are not clearly known, according to the type of malignancy or chemotherapeutic regimens. However, preemptive therapy should be considered in high-risk patients with detectable serum HBV DNA, including lymphoma receiving rituximab-based chemotherapy and leukemia undergoing hematopoietic stem cell transplantation. The need for preemptive treatment, however, may be determined based on periodic (*e.g.*, monthly or bimonthly) monitoring of the serum HBV DNA in patients who are negative for serum HBV DNA prior to chemotherapy.

To date, there are three recently updated practice guidelines from major liver societies worldwide as summarized below. The recommendations for the management of HBV reactivation are largely similar among these guidelines, but there are some minor discrepancies in the details. Table 2 summarizes and compares the differences among these guidelines.

LESSONS FROM RECENT REPORTS

Because the clinical practice guidelines for HBV infection, including the management of HBV reactivation, were released by AASLD (2009), EASL (2012) and APASL (2012)[1,40,43], this section mainly covers newer reports, released after these guidelines. During the past couple of years, research interests in the field of HBV reactivation have focused on lymphoma, particularly the risk of HBV reactivation with rituximab-based treatment in occult/past HBV infection. A retrospective study by Pei *et al*[44] (n = 29) reported that decreases in the anti-HBs titer after rituximab treatment were observed, especially in HBsAg-negative patients with low baseline anti-HBs titers (< 100 mIU/mL). This seems relevant, as previous reports showed that the absence or presence of low titers of anti-HBs was associated with the risk of HBV reactivation among lymphoma patients under rituximab-containing treatments[17,26,29]. Although the demonstration of decreasing anti-HBs titer was intriguing in the study by Pei *et al*[44], the small number of study subjects prevented the investigators from providing clearer and more robust evidence regarding the role of changing anti-HBs titers in the dynamic risk of HBV reactivation in rituximab-treated lymphoma patients. Indeed, hepatitis flares after chemotherapy occurred in only 6 patients. Instead, the study presented a provisional association of the risk of HBV reactivation with anti-HBs, in which the risk of hepatitis flares was higher in patients with lost anti-HBs after chemotherapy (4/8 *vs* 2/21, P = 0.033). A recent multi-center prospective study from Taiwan demonstrated HBV reactivation under rituximab-based chemotherapy occurred in 17 out of 150 lymphoma patients with anti-HBc (HBsAg-negative), whilst HBV DNA was being monitored at baseline, at the start of every chemotherapy cycle, and every 4 wk after completion of chemotherapy[45]. In this study, hepatitis flare (defined as increase in ALT of 3 fold or higher, exceeding 100 IU/L) was more frequently associated with re-appearance of HBsAg after reactivation of HBV. Regarding the risk of reactivation of occult/past HBV infection in lymphoma patients, a meta-analysis by Dong *et al*[46], including 971 lymphoma patients from 9 studies, demonstrated that the relative risk of HBV reactivation by rituximab-based treatments was 5.52 (95%CI: 2.05-14.85, P = 0.0007) in patients with occult/past infections (anti-HBc IgG-positive, HBsAg-negative). Although the obvious heterogeneity in the included studies and presence of publication bias should be prudently taken into consideration when interpreting the results, this meta-analysis contributed further supporting evidence of the HBV reactivation risk in the lymphoma patient population with occult/past HBV infections. Another retrospective study from Japan included 109 HBsAg-negative patients (59 with anti-HBc) undergoing chemotherapy for either lymphoma or multiple myeloma, in which serum HBV DNA was quantified monthly during and after chemotherapy in each study subject[47]. During the median follow-up period of 20.5 mo, four out of 59 anti-HBc-positive patients

Table 2 Comparison of prophylactic strategies against the reactivation of hepatitis B with recent major guidelines

	AASLD (2009)[1]	EASL (2012)[40]	APASL (2012)[43]
Screening tests	HBsAg, anti-HBc	HBsAg, anti-HBc	HBsAg; anti-HBc in rituximab- or anti-TNF-α-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 or telbivudine if duration of treatment ≤ 12 mo and baseline HBV DNA is undetectable; tenofovir or 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 or tenofovir if high HBV DNA and/or lengthy, repeated cycles of immunosuppression are planned	Lamivudine; entecavir or tenofovir can be used
Occult/past infection	Monitor HBV DNA; treat if HBV DNA becomes detectable	Test for HBV DNA; if HBV DNA-positive, treat similarly to HBsAg-positive 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

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; APASL: Asian Pacific Association for the Study of the Liver; HBsAg: Hepatitis B surface antigen; anti-HBc: Anti-hepatitis B core antibody; TNF: Tumor necrosis factor; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

developed HBV reactivation, and three of them were negative for anti-HBs. Due to the small sample size, the statistical significance of anti-HBc for HBV reactivation was not proven. However, the authors underscored that the HBV DNA should be monitored during and after chemotherapy in order to detect HBV reactivation earlier. In line with these reports, a cost-effectiveness analysis on HBV screening before chemotherapy for lymphoma was recently conducted in Canada[48]. Out of the three strategies (screening all patients, screening high-risk patients for HBV infections, and no screening), a decision tree model analysis revealed that the rate of HBV reactivation was reduced to one-tenth with screening all patients, resulting in lower costs among patients receiving rituximab-based chemotherapy for lymphoma. Prior to this report, another cost-effectiveness study on HBV screening from Australia was published[49]; its results indicated that universal HBV screening was not cost-effective in patients with solid tumors, specifically in hypothetical patient cohorts receiving adjuvant chemotherapy for early breast cancer or palliative chemotherapy for advanced non-small cell lung cancer. However, cost-effectiveness was maintained in limited HBsAg screening in the population with adjuvant chemotherapy. Taken together, cost-effectiveness seems to be dependent on the different risks of HBV reactivation in different clinical settings.

The proper choice of an antiviral agent is another important issue to be resolved. Lamivudine has been widely accepted as a representative antiviral agent for preemptive therapy in HBsAg-positive patients undergoing chemotherapy, based on the results of previous randomized controlled trials, as described earlier. However, the development of resistance to lamivudine has been a major concern in its preemptive use[50-52]. Newer potent antiviral agents with high genetic barriers to resistance have been launched in recent years, and their efficacy in the preemptive setting needs to be further investigated. A recent multinational retrospective study in Asia (n = 340) revealed that breakthrough HBV reactivation was observed in more than 20% of lamivudine-treated HBsAg-positive lymphoma patients undergoing rituximab-containing chemotherapy[53]. In this study, the entecavir-treated group showed a reduced rate of HBV reactivation compared with the lamivudine-treated group (6.3% *vs* 39.3%, P < 0.05). The optimal duration of preemptive antiviral therapy also remains unclear. In the rituximab era, late HBV reactivation has been reported up to 170 d after the last dose of rituximab-containing chemotherapy[17]. A recent retrospective study by Chen *et al*[54] reported that HBV reactivation occurred up to 230 d after the last dose of rituximab. It seems necessary to monitor the serum HBV DNA titers regularly during and after the completion of any rituximab-based chemotherapy in lymphoma patients as well as to consider longer durations of preemptive antiviral therapies, especially among those receiving prolonged chemotherapy. An intriguing case report from Italy showed that viral breakthrough occurred during entecavir prophylaxis in the absence of viral mutations in a patient with chronic lymphocytic leukemia under bendamustine therapy[55]. The authors argued that this uncontrolled viral replication resulted from "immunological escape" phenomenon under persistent and severe immune system impairment, necessitating combination treatment[56]. Although this combination strategy was advocated by a case report by the same author group[57], it requires further investigation.

Recently, a randomized controlled trial of prophylactic entecavir for lymphoma patients with resolved

HBV infection was reported[58]. Serum HBV DNA was undetectable in 62.5% of the lymphoma patients at baseline. Patients were randomly assigned to either entecavir prophylaxis (started before chemotherapy until 3 mo after chemotherapy; n = 41) or therapeutic entecavir at the time of HBV reactivation (n = 39). The incidences of HBV reactivation at 18 mo of follow-up were 4.3% in the treatment group and 25.9% in the control group (P = 0.019). Although this study provided valuable information regarding preemptive antiviral therapy in lymphoma patients with "resolved" HBV infections, the study design seems debatable because 30 patients (37.5%) had "occult" HBV infections and were positive for serum HBV DNA. Those patients require preemptive antiviral therapy from the beginning of chemotherapy, rather than deferred treatment, according to the latest EASL guideline[40]. However, this study began in 2009, when there was no recommendation for a preemptive therapy in patients with occult/past infections. Thus, further studies with updated designs are warranted to support the findings of this trial.

Lastly, an interesting report from Singapore on the risk of HBV reactivation in patients with solid tumors was published recently. Ling *et al*[59] reported in their large-scale retrospective analysis (n = 1149) that only 0.3% (3 out of 1149) of patients developed HBV reactivation if they had not been screened for HBV infection prior to chemotherapy and instead received a doxorubicin-based regimen; on the other hand, those patients who received oxaliplatin/irinotecan-based or carboplatin plus gemcitabine capecitabine chemotherapy did not develop HBV reactivations. The authors argued that routine screening and preemptive therapy for lower-risk chemotherapy regimens may not be necessary, even in HBV-endemic regions.

UNRESOLVED ISSUES AND FUTURE PERSPECTIVES

What is (are) the proper antiviral agent(s) for preemptive treatment?

The current recommendations on the preemptive antiviral therapy are largely based on previous data from clinical trials of lamivudine in HBsAg-positive patients. Published studies, especially randomized trials, are mostly limited to lamivudine, both in lymphoma and in solid tumors[14,38,60]. A systematic review also concluded that preemptive lamivudine therapy reduced the risk of HBV reactivation-related hepatitis by approximately 80%[9]. However, the most concerning and serious drawback of lamivudine therapy is the emergence of resistant strains to lamivudine, as mentioned earlier[14]. In addition, the failure of prophylaxis with lamivudine due to virologic breakthroughs and cases of withdrawal hepatitis has been reported, especially if the baseline viral load was high or rituximab was used[61]. More potent antiviral agents with a high genetic barrier might be preferable, particularly in cases of high-risk patients for HBV reactivation or after prolonged chemotherapy. To date, however, only limited data exist on the prophylactic efficacy of such newer agents. A recent retrospective study from China reported the superiority of entecavir (n = 34) compared to lamivudine (n = 89) in preventing HBV reactivation in lymphoma patents[42]. Another multicenter retrospective study included a heterogeneous population with lymphoma and various solid tumors (n = 241), the results of which are currently available as an abstract; the results of that study showed that prophylaxis with entecavir (n = 31) or telbivudine (n = 124) was more effective than with lamivudine (n = 86). The HBV reactivation rate was not significantly different between entecavir and telbivudine[62]. A multicenter, randomized controlled trial comparing entecavir and lamivudine in patients with lymphoma or solid tumors is in progress, and the results are anticipated with keen interest (NCT01580202).

What is the optimal duration of preemptive antiviral therapy?

Discontinuation of lamivudine prophylaxis at 3 mo after the completion of chemotherapy resulted in an HBV reactivation rate of 24% in a previous study, especially among patients with high baseline HBV DNA levels[41]. The EASL guidelines strongly recommend continuing preemptive therapy for 12 mo in HBsAg-positive patients after the cessation of chemotherapy based on previous studies[9,14], with the level of evidence "A" and the grade of recommendation "1"[40]. However, neither of the two references for this recommendation provided sufficient evidence to support the preference of 12 mo of maintaining preemptive therapy over a shorter treatment duration. Furthermore, these references were based on studies using lamivudine[9,14], and currently, the data are insufficient to determine the optimal durations of more potent antiviral agents, such as entecavir or tenofovir. The AASLD guideline (2009) recommended a graded approach, in which lamivudine or telbivudine could be used for a planned duration of less than 12 mo, while entecavir or tenofovir was recommended for a longer duration of therapy[1]. However, supporting data were not sufficient for these recommendations. In addition, HBsAg titer is used for prediction of treatment response to peginterferon[40]. However, use of HBsAg quantification is currently not supported by sufficient evidence in terms of prediction of response or determination of duration of prophylactic antiviral therapy for HBV reactivation.

Prophylaxis in patients with occult/past infections undergoing chemotherapy

Based on the most recent reports described earlier, screening for evidence of past HBV infection in HBsAg-negative patients seems reasonable among high-risk patients, including those undergoing rituximab-based chemotherapy or with hematologic malignancies, especially in HBV-endemic areas. The randomized controlled trial of entecavir prophylaxis in patients with lymphoma and resolved HBV infections conveyed important messages

for the management of patients at potential risk of HBV reactivation in the rituximab era[58]. However, its study design, which included the possibility of assigning patients with occult infections with detectable serum HBV DNA to the control (or deferred treatment) arm, made its conclusion somewhat questionable, as discussed earlier. Further compelling evidence is urgently required to resolve this unmet need.

CONCLUSION

Patients with HBV infections who receive anticancer chemotherapy are at risk of HBV reactivation during and after the completion of chemotherapy. Recent guidelines recommend preemptive antiviral therapy for HBsAg-positive patients undergoing chemotherapy, irrespective of their baseline viral load. However, the proper choice of antiviral agent and the optimal treatment duration are still under debate. Recently, several studies have reported the risk of reactivation in occult/past HBV infections. Based on the aforementioned observational studies and cost-effectiveness analyses, screening for occult/past infections in HBsAg-negative patients is strongly recommended, especially among lymphoma patients who receive rituximab-based chemotherapy or patients undergoing intensive immunosuppression. Again, the proper antiviral agent(s) and the optimal treatment duration remain unclear. Randomized controlled trials to compare different antiviral agents in homogeneous populations are urgently warranted to establish management strategies for the prevention of HBV reactivation in at-risk patients undergoing chemotherapy.

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