Why, When, and How to Prevent Hepatitis B Virus Reactivation in Cancer Patients Undergoing Chemotherapy

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Key Words

Hepatitis B virus, reactivation, chemotherapy, cancer

Abstract

Hepatitis B virus (HBV) reactivation is a serious clinical problem in HBV carriers undergoing chemotherapy. The clinical course of HBV reactivation can be separated into 2 phases: 1) an increase in HBV replication and 2) hepatic injury. Patients with resolved HBV infections (negative for hepatitis B surface antigen [HBsAg], and positive for both hepatitis B core antibody [anti-HBc] and/or hepatitis B surface antibody) can experience HBV reactivation, and Western guidelines recommend that not only HBsAg but also anti-HBc be screened before initiation of chemotherapy or immunosuppressive therapy. Several meta-analyses have repeatedly confirmed the prophylactic role of lamivudine in preventing HBV reactivation. In conclusion, screening for HBV is required before chemotherapy, and prophylactic antiviral therapy can reduce not only the incidence of HBV reactivation but also HBV-related morbidity and mortality. (*JNCCN* 2011;9:465–477)

Epidemiology of Hepatitis B Virus

Hepatitis B virus (HBV) has infected more than 2 billion people worldwide, and approximately 350 million patients worldwide have chronic HBV infection.^{1,2} In

the United States, carriers of chronic hepatitis B surface antigen (HBsAg) continue to increase as a consequence of increasing immigration from HBV endemic areas, such as East Asia, South Asia, and Africa. The United States comprises 1.5 million of the worldwide chronic HBsAg carriers.³ In Korea, which is regarded as an endemic area of HBV infection, a nationwide survey revealed an HBsAg prevalence of 5.1% in men and 4.1% in women.⁴

Reactivation of HBV has been well documented in infected patients receiving chemotherapy for cancer treatment.^{5–8} With the increasing use of chemotherapy, reactivation of HBV has become a serious cause of morbidity and mortality. The frequency of HBV reactivation among patients with cancer who are HBsAg-positive is expected to be the same, regardless of the geographic area.⁵ However, the frequency of HBV reactivation in a given population differs geographically because the prevalence of HBV infection varies among different populations (from 10%–25% in highly endemic areas, to < 1% in other areas).^{9–11}

Besides geographic differences, different types of cancer, different chemotherapeutic regimens, different use of antiviral agents, and the absence of well-designed prospective trials have hampered the establishment of preventive strategies for HBV reactivation. This article summarizes the current status of HBV reactivation secondary to chemotherapy, and proposes a prophylactic strategy for HBV reactivation.

Diagnosis of HBV Reactivation

Chemotherapy-induced HBV reactivation has a broad range of manifestations, ranging from asymptomatic rises in serum aminotransferase levels to fatal fulminant

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hepatitis.¹² HBV reactivation is characterized by elevated levels of serum HBV DNA, abnormal liver function tests, and clinical hepatitis with different degrees of severity.¹⁰ Diverse definitions for HBV reactivation have been used in previous studies, which has prevented an exact comparison of HBV reactivation. An early report described 2 types of HBV reactivation¹³: 1) patients who were HBsAg-positive experiencing an increase in serum HBsAg titer, and 2) patients who were HBsAg-negative/hepatitis B surface antibody (anti-HBs)-positive with declining anti-HBs and reappearance of HBsAg (seroreversion). To reflect these characteristics, the most widely used definition of HBV reactivation is based on the criteria proposed by Lok et al.¹⁰ and modified by Yeo et al.¹⁴ According to this criteria, the definition of HBV reactivation should include 2 components: 1) the presence of hepatitis, and 2) hepatitis attributed to HBV reactivation. The definition of hepatitis is a 3-fold or greater increase in alanine aminotransferase (ALT) that exceeds the upper limit of normal. Hepatitis attributable to HBV reactivation is defined as a 10-fold or greater increase in HBV DNA levels compared with baseline levels, or an absolute increase in the HBV DNA level that exceeds 10^5 copies/mL in the absence of another systemic infection. Exact baseline evaluation and close monitoring of ALT and HBV DNA levels is mandatory for early diagnosis and prompt management of HBV reactivation.¹⁵

Pathogenesis of HBV Reactivation

Theoretically, administering any immunosuppressive therapy to patients with chronic HBV infection may allow the virus to escape immune control, leading to increased HBV replication and a marked increase in HBV antigen expression within hepatocytes.¹⁶ Approximately 50% of HBV reactivation occurs during the recovery phase from immunosuppression, 10 to 90 days after discontinuation of cytotoxic chemotherapy or immunosuppressive agents,¹⁷ and the other 50% occurs during immunosuppression. Hence, 2 distinct pathogenic mechanisms are believed to be associated with HBV reactivation, according to the time of onset.¹⁸ The first mechanism of reactivation during the recovery phase is an exaggerated immunologic response to HBV-infected hepatocytes. During im-

munosuppression from cytotoxic chemotherapy or immunosuppressive agents, such as glucocorticoids, viral replication increases, leading to widespread infection of hepatocytes. However, in this period, overt hepatocellular injury does not occur because cytotoxic T cells are suppressed. After immunosuppression is withdrawn, infected hepatocytes with recognizable viral antigens on their surface might be exposed and cleared by cytotoxic T cells with an exaggerated immunologic response, leading to hepatic necrosis and clinically relevant hepatitis. This mechanism is supported by the observation that HBV carriers can have an increased concentration of HBsAg and HBV DNA during immunosuppressive treatment, followed by decreased viral replication on withdrawal of immunosuppression, which is attributed to immune function.^{12,18,19}

The second pathogenic mechanism of HBV reactivation during immunosuppression is associated with immunosuppression-induced augmentation of HBV replication that is directly toxic to host hepatocytes. Immunosuppressive agents may have a more direct stimulatory effect on viral replication.²⁰ *In vitro*, glucocorticoids increase HBV DNA and RNA production by stimulating HBV transcription^{21,22} through binding to the glucocorticoid-responsive element and augmenting HBV enhancer I. In general, the first mechanism is considered to be a more important contributor for HBV reactivation.

Frequency and Clinical Features of HBV Reactivation

The frequencies of HBV reactivation are difficult to estimate from published studies because of the different definitions of HBV reactivation, heterogeneous cancer types, heterogeneous chemotherapy regimens, and regional differences in HBV prevalence. As the role of prophylactic lamivudine has been elucidated in patients with cancer who are HBsAg-positive, estimating the natural frequency of HBV reactivation has become more difficult. In early prospective reports, the frequencies of HBV reactivation were reported to be 37.8%²³ in a Japanese study, and 47%¹⁰ and 19%¹⁴ in Hong Kong studies. The frequency of HBV reactivation may decrease as many guidelines^{24–27} have begun recommending the use of prophylactic antiviral agents before chemotherapy.

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The clinical features of HBV reactivation vary from asymptomatic hepatitis to fulminant hepatic failure leading to death. The mortality rates have been reported to range from 5% to 41%.^{10-12,23,28} The clinical course of HBV reactivation can be separated into 2 phases²⁹: 1) increase in HBV replication, and 2) hepatic injury (Figure 1). In the first phase, HBV DNA or the HBsAg titer increases as viral replication occurs soon after initiating chemotherapy or immunosuppressive agents. Hepatitis B e antigen (HBeAg) may reappear in patients who are initially HBeAg-negative. The second phase of reactivation usually starts when immunosuppression is withdrawn or decreased. In the second phase, serum ALT levels increase as hepatocellular damage rises, and HBV DNA may begin to decrease. Immune-mediated destruction of HBV-infected hepatocytes manifests clinically as hepatitis, hepatic failure, and even death.^{5,29,30} Patients with cirrhosis are more likely to develop hepatic decompensation, resulting in hepatic failure.⁵

Risk Factors for HBV Reactivation: Patient Factors, Cancer Type, and Treatment Factors

Identifying risk factors for HBV reactivation is clinically important because it provides guidance for prevention strategies. Several studies have reported the risk factors for HBV reactivation (Table 1). However, the risk factors have not been completely clarified because of the small sample size of each study and different clinical settings.

Early reports have failed to show that prechemotherapy viral load is a predictor for HBV reactivation.

Figure 1 Clinical course of HBV reactivation. The first phase is characterized by enhanced HBV viral replication, and the second phase is characterized by an enhanced host immune response to HBV-infected hepatocytes and hepatic injury. Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus. From Lau GK. Hepatitis B reactivation after chemotherapy: two decades of clinical research. *Hepatol Int* 2008;2:154; with permission.

tion.^{14,15,31} However, with the introduction of highly sensitive assays, such as real-time polymerase chain reaction, recent studies have consistently reported that a high HBV viral load before chemotherapy is significantly associated with HBV reactivation.^{30,32,33} Different studies have used different assays in measuring the HBV viral load,⁵ and therefore a standardized method to measure HBV viral load with a variable range of detection may be needed.

Baseline prechemotherapy HBeAg positivity has been confirmed as a risk factor for HBV reactivation in univariate^{10,14} and multivariate analyses.^{34,35} However, HBeAg positivity has not been shown to

Table 1 Risk Factors of HBV Reactivation in Patients With Cancer Undergoing Chemotherapy Based on Multivariate Analysis

Reference	Cancer	No. of HBsAg Carrier Studies	Rate of HBV Reactivation	Risk Factors
Lau et al. ³⁰	Lymphoma	23	45%	Baseline high HBV DNA level
Nagamatsu et al. ³⁵	HCC	33	24%	HBeAg positivity
Yeo et al. ²⁸	HCC	102	36%	Baseline high ALT level
Yeo et al. ³³	Various	138	26%	Lymphoma or breast cancer Use of steroid Baseline high HBV DNA level
Hui et al. ³⁹	Lymphoma	22	41%	High intrahepatic CCC DNA level
Jang et al. ³¹	HCC	146	22%	HBeAg positivity

Abbreviations: ALT, alanine aminotransferase; CCC DNA, covalently closed circular DNA; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

be a risk factor in other studies,^{36,37} but instead may be related to the presence of precore/core promoter HBV mutants.³⁸ One study showed that intrahepatic, covalently closed circular (CCC) DNA, which is a key intermediate in HBV replication, was associated with HBV reactivation.³⁹ The overall accuracy of intrahepatic CCC DNA in predicting HBV reactivation was 88.9%, with a sensitivity of 77.8% and a specificity of 100%. However, quantification of CCC DNA requires a liver biopsy, which has inherent sampling error, and measuring the CCC DNA has limitations in its clinical applicability, especially for patients with coagulopathies. Many studies have been conducted recently to identify a validating marker to replace CCC DNA, such as the quantification of serum HBsAg.⁴⁰

Apart from viral factors, the rate of HBV reactivation depends on the type of malignancy and the chemotherapeutic agents used. The 2 most common clinical settings in which HBV reactivation has been reported are during chemotherapy for lymphoma and during immunosuppressive treatment after hematopoietic stem cell transplantation (HSCT). However, HBV reactivation has also been reported in other solid tumors, including breast cancer,^{32,41,42} hepatocellular carcinoma (HCC),^{34,43} nasopharyngeal cancer,⁴⁴ small cell lung cancer,⁴⁵ and neuroendocrine tumors.⁴⁵ Whether the relative lack of reports in other types of malignancies is the result of a lower degree of immunosuppression in other cancers or a lower incidence of other cancers in HBV endemic areas is unknown.

Anthracyclines and glucocorticoids are well-known risk factors for HBV reactivation. Table 2 summarizes the reported chemotherapeutic agents that have been related to HBV reactivation. Notably, HBV reactivation can be caused by not only conventional cytotoxic chemotherapeutic agents but also molecular targeted agents. Rituximab, a chimeric monoclonal antibody directed against CD20 in lymphoid cells, has been used in the treatment of lymphomas, and has been associated with HBV reactivation when used as a single agent^{46–48} or in combination with cytotoxic chemotherapeutic agents.^{49–57} HBV reactivation has also been reported in patients with hematologic malignancies treated with alemtuzumab, a humanized monoclonal antibody directed against CD52 in lymphoid cells.^{58,59} Rituximab and alemtuzumab have induced

profound and durable B- and T-cell depletion,^{60,61} and B cells may modulate the priming cytotoxic T-cell response to HBV infection.⁶²

Three case reports have also shown imatinib mesylate, a tyrosine kinase inhibitor for bcr-abl and c-kit, to be related to HBV reactivation.^{63–65} Sorafenib, the first agent documenting survival benefit in advanced HCC,^{66,67} has been used in the treatment of HCC, but HBV reactivation has not been reported in studies using sorafenib in patients with HCC.^{66–69} To the authors' best knowledge, HBV reactivation has not been reported in patients treated with tyrosine kinase inhibitors other than imatinib. HBV reactivation in patients with nonhematologic malignancies treated with commonly used molecular targeted agents, including gefitinib, erlotinib, sunitinib, trastuzumab, bevacizumab, and cetuximab, has not yet been elucidated. The mammalian target of rapamycin (mTOR) inhibitors, such as FK506, are already used to treat transplant rejection, and are beginning to be used as chemotherapeutic agents. Among the mTOR inhibitors, RAD001 (everolimus) has been reported to be associated with HBV reactivation.⁷⁰ Further data are needed to identify the characteristics of HBV reactivation in patients treated with molecular targeted agents and to develop a prophylactic strategy.

HBV Reactivation in Patients Who Are HBsAg-Negative

Patients with resolved HBV infections (HBsAg-negative, and positive for hepatitis B core antibody [anti-HBc] and/or anti-HBs) can experience HBV reactivation,^{10,13,71–75} but this occurs less commonly than in patients who are HBsAg-positive. However, with the recent increased use of rituximab, reports of HBV reactivation after treatment with this agent in patients with resolved HBV infections have also increased.^{46–51,54–56,76} Based on case series, nearly 20% of patients died of hepatic failure.⁵⁰ HBV reactivation has also been associated with HSCT in patients with hematologic malignancies with resolved HBV infections.^{77–79} In endemic areas, such as the Asian-Pacific region, vertical or perinatal transmission is associated with a higher rate of progression to chronic hepatitis B (90%)^{80,81} and is the predominant form of HBV infection; a relatively lower portion of patients have resolved HBV infections. However, attention should be

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Table 2 Chemotherapeutic Agents Associated With Hepatitis B Virus Reactivation

	Agents	References
Corticosteroid	Prednisolone	12–14, 19, 39, 52, 54–57, 97–104
	Dexamethasone	12, 55, 99, 101–103
	Methylprednisolone	12, 105
Anthracycline	Doxorubicin	14, 28, 32, 39, 52, 54, 56, 57, 97–103, 106
	Epirubicin	14, 32, 100, 107
	Daunorubicin	13, 102, 105
	Idarubicin	98
Antitumor metabolite	5-Fluorouracil	14, 28, 32, 99
	Methotrexate	13, 14, 39, 97, 99, 101, 102, 104
	Cytarabine	13, 49, 98, 101, 104, 105
Alkylating agents	Cyclophosphamide	13, 14, 19, 32, 39, 52, 54, 56, 57, 97–104, 106
	Chlorambucil	101, 104
	Ifosfamide	39
	Gemcitabine	14, 99, 108, 109
	Mercaptopurine	104, 105
Vinca alkaloid	Vincristine	13, 14, 19, 39, 52, 54, 56, 57, 97–104
	Vinblastine	14, 39, 97, 105
Taxane	Paclitaxel	14
	Docetaxel	14, 32, 106, 107
Platinum	Cisplatin	19, 28, 99, 101, 106
	Carboplatin	14
Antitumor antibiotics	Mitomycin-C	14, 32
	Bleomycin	19, 39, 97, 101–103
	Actinomycin D	19
Other cytotoxic agents	Etoposide	14, 39, 55, 101, 108
	Procarbazine	13, 39, 97, 99
	Dacarbazine	97
	Lomustine	99
	Fludarabine	37
Monoclonal antibodies	Rituximab	46–57
	Alemtuzumab	58, 59
Tyrosine kinase inhibitors	Imatinib	63–65
Immune modulators	Thalidomide	110
	Interferon	28, 49, 111
mTOR inhibitor	Everolimus	70

Data from Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006;43:214.

given to patients with resolved HBV infections, especially those undergoing rituximab treatment or HSCT.

The European and United States guidelines for the management of chronic hepatitis B recommend that not only HBsAg but also anti-HBc antibodies

be screened before initiation of chemotherapy or immunosuppressive therapy.^{24,27} However, the Korean guidelines do not recommend routine screening for anti-HBc antibodies²⁵ because most HBV infections result from vertical transmission in Korea.⁸¹ The Eu-

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ropean guidelines²⁴ recommend that patients who are HBsAg-negative with positive anti-HBc and undetectable HBV DNA in the serum who undergo chemotherapy and/or immunosuppression be monitored carefully with ALT and HBV DNA testing and treated with antiviral therapy on confirmation of HBV reactivation before ALT elevation.²⁴ The United States guidelines do not recommend routine prophylaxis for patients with resolved HBV because not enough information is available on this issue.²⁷ The optimal approach to managing patients with resolved HBV infection must be elucidated through future research in terms of clinical benefit and cost-effectiveness. Comparison of the HBV reactivation rates between the patients who are HBsAg-positive and resolved HBV infections is also warranted, because this is likely to have significant implications in the United States.

Effect of Prophylactic Antiviral Therapy

Many studies have shown the effectiveness of prophylactic antiviral therapy in reducing the incidence of HBV reactivation. Table 3 summarizes the current studies that have compared patients who did and did not receive prophylactic lamivudine. Several meta-analyses have repeatedly confirmed the prophylactic role of lamivudine.^{6,7,82,83} Loomba et al.⁶ analyzed 14 studies and reported the results of a meta-analysis, concluding that preventive therapy with lamivudine for patients who are HBsAg-positive and are undergoing chemotherapy may reduce the risk of HBV reactivation and HBV-associated morbidity and mortality. With preventive lamivudine, the relative risk for HBV reactivation ranges from 0.00 to 0.21, favoring prophylactic lamivudine.

Kohrt et al.⁷ and Katz et al.⁸² also reported similar results of meta-analyses. Although these meta-analyses were conducted using many retrospective studies, the analyzed studies were consistently in favor of prophylactic lamivudine. As a result, the consensus is emerging that prophylaxis with antiviral agents is essential for patients who are HBsAg-positive undergoing chemotherapy.

Recently, the authors retrospectively reviewed the medical records of 3530 patients with stages I through III breast cancer, and examined the efficacy of prophylactic lamivudine compared with historical controls. Among the 3530 patients, 171 (4.8%) were HBsAg-positive and from the authors' insti-

tute, which was located in a HBV endemic area. Of the 171 patients, 70 patients received lamivudine prophylaxis and 101 patients did not. Hepatotoxicities occurred more frequently in the nonprophylactic group (2.9% vs. 12.9; $P = .027$), as did HBV reactivation (6.9% vs. 1.4%; $P = .143$; unpublished data).

How to Use Prophylactic Antiviral Therapy: Optimal Duration and Drug

Because the main mechanism of nucleos(t)ide analogues in inhibiting viral replication is direct suppression of HBV DNA polymerase activity, antiviral potency has been little affected by host immune status. Data are still insufficient on the optimal duration of prophylactic antiviral therapy. Premature withdrawal of lamivudine could lead to a rapid rebound of viral replication, resulting in HBV-related mortality.⁸⁴ However, prolonged use of lamivudine is associated with an increasing likelihood of developing lamivudine-resistant HBV variants with YMDD mutants^{85,86} (from 24% at 1 year to 38% at 2 years, 50% at 3 years, and 67% at 4 years).^{87,88} Several patients who developed lamivudine-resistant mutations, such as a YMDD mutant during lamivudine prophylaxis, have been reported.⁸⁹⁻⁹² Compared with patients with chronic hepatitis B, a similar rate of developing genotypic YMDD mutants was observed in patients with lymphoma.⁹³

Hence, the current guidelines recommend discontinuing prophylactic lamivudine as soon as possible after restoration of host immune status, and setting a limit to the duration of lamivudine therapy. However, many guidelines differ in the duration of treatment, from at least 3 to 12 months after completion of chemotherapy. Hui et al.⁹⁴ studied the occurrence of HBV reactivation after prophylactic lamivudine, and found that 23.9% of patients (11/46) receiving prophylactic lamivudine 3 months after completion of chemotherapy experienced HBV reactivation, and that high baseline HBV DNA ($> 10^4$ copies/mL) and HBeAg were significantly associated with HBV reactivation. Based on this study, patients with high baseline HBV DNA or HBeAg should be followed up closely for a longer period of lamivudine prophylaxis with the same end point of immunocompetent patients, such as HBeAg seroconversion. In the authors' clinical practice, prophylactic lamivudine is started at least 1 week before chemotherapy, and continued for

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Table 3 Current Studies on the Role of Prophylactic Lamivudine

Studies	Cancer	Country	Prophylaxis Schedule	Incidence of HBV Reactivation Lamivudine vs. No Lamivudine	Comments
<i>Retrospective Comparative Case Series</i>					
Lim et al. ⁹⁹	Various	Singapore	Before start of chemotherapy Until completion of chemotherapy	0.0% (0/16) vs. 36.8% (7/19)	Dose: 100–300 mg
Persico et al. ¹¹²	Lymphoma	Italy	During and after chemotherapy 2 mo after completion of chemotherapy	0.0% (0/3) vs. 57.1% (12/21)	
Lee et al. ¹¹³	Lymphoma	Korea	Details not reported	9.1% (1/11) vs. 85.0% (17/20)	
Leaw et al. ¹¹⁴	Lymphoma	Taiwan	Start of chemotherapy 1 mo after completion of chemotherapy	0.0% (0/11) vs. 32.1% (17/53)	
Nagamatsu et al. ⁴³	HCC	Japan	4 wk before chemotherapy Until completion of chemotherapy	0.0% (0/8) vs. 66.7% (6/9)	TACE, all patients were HBeAg-positive
Ozguroglu et al. ¹¹⁵	Lymphoma	Turkey	Details not reported	0.0% (0/4) vs. 62.5% (5/8)	
<i>Prospective Cohort Studies With Historical Control Groups</i>					
Dai et al. ¹⁰⁶	Breast	Taiwan	Start of chemotherapy 1 mo after completion of chemotherapy	0.0% (0/11) vs. 55.6% (5/9)	
Yeo et al. ¹¹⁶	Various	Hong Kong	1 wk before chemotherapy 2 mo after completion of chemotherapy	4.6% (3/65) vs. 24.4% (47/193)	
Yeo et al. ⁴²	Breast	Hong Kong	1 wk before chemotherapy 2 mo after completion of chemotherapy	6.5% (2/31) vs. 31.1% (19/61)	
Yeo et al. ⁴⁴	Nasopharyngeal	Hong Kong	1 wk before chemotherapy 2 mo after completion of chemotherapy	0.0% (0/16) vs. 28.6% (6/21)	
<i>Prospective Cohort Studies With Control Groups</i>					
Shibolet et al. ⁹⁷	Various	Israel	1–60 d before chemotherapy 0.5–24 mo after completion of chemotherapy	0.0% (0/9) vs. 40.0% (2/5)	Dose: 150 mg
Idilman et al. ⁹⁸	Hematologic	Turkey	Start of chemotherapy 12 mo after completion of chemotherapy	0.0% (0/8) vs. 50.0% (5/10)	
<i>Randomized Controlled Studies</i>					
Lau et al. ¹⁰⁰	Lymphoma	China	1 wk before chemotherapy At least 6 wk after completion of chemotherapy	0.0% (0/15) vs. 53.3% (8/15)	
Jang et al. ³⁴	HCC	Korea	Start of chemotherapy 12 mo after completion of chemotherapy	2.8% (1/36) vs. 29.7% (11/37)	TACE

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Table 4 Comparison of Current Guidelines for Hepatitis B Virus Reactivation

	United States (AASLD²⁷)	Europe (EASL²⁴)	Asian-Pacific (APASL²⁶)	Korea (KASL²⁵)
Screening indication	Patients who are at high risk for HBV infection	All candidates for chemotherapy	All candidates for chemotherapy	All candidates for chemotherapy
Screening parameters	HBsAg and anti-HBc	HBsAg and anti-HBc	HBsAg	HBsAg
Screening timing	Before initiation of chemotherapy	Before initiation of chemotherapy	Before initiation of chemotherapy	Before initiation of chemotherapy
Indication of PAT	HBV carriers	HBsAg(+) regardless of HBV DNA Recipients of anti-HBc-positive liver graft	HBsAg(+)	HBsAg(+)
Timing of starting PAT	With start of chemotherapy	During chemotherapy	Before the start of chemotherapy	Before or with start of chemotherapy
Agent for PAT	Lamivudine or telbivudine, if the anticipated duration of treatment is short (< 12 mo) Entecavir or tenofovir is preferred if longer duration of treatment is anticipated	Lamivudine for the HBsAg(+) patients with low HBV DNA levels and low risk of resistance Entecavir or tenofovir for the HBsAg(+) patients with high HBV DNA level	Lamivudine (other antiviral agents can also be used)	Not specified
Duration of PAT	For 6 mo after completion of therapy, in case of low baseline HBV DNA (< 2000 IU/mL) Until reaching treatment end points of immunocompetent patients, in case of high baseline HBV DNA (> 2000 IU/mL)	For 12 mo after completion of therapy	At least 12 wk after completion of therapy	For 3–6 mo after completion of therapy
Other comments	Interferon- α should be avoided in view of the bone marrow suppressive effect	Vaccination against HBV seronegative patients is highly recommended		

Abbreviations: AASLD, American Association for the Study of Liver Diseases; Anti-HBc, hepatitis B core antibody; APASL, Asian-Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; KASL, Korean Association for the Study of the Liver; PAT, prophylactic antiviral therapy.

6 months after completion of chemotherapy. Table 4 summarizes the current guidelines for HBV reactivation, and Figure 2 is a proposed practical algorithm for the prevention of HBV reactivation.

Lamivudine-resistant HBV variants can be associated with rapid clinical deterioration after transplantation during lamivudine prophylaxis,^{89,91} and raises concerns. To avoid lamivudine resistance, alternative nucleos(t)ides analogues, such as adefovir, tenofovir, entecavir, or telbivudine, are promising for prophylactic use,²⁹ although no data are available on adefovir and entecavir

as prophylactic treatment for preventing HBV reactivation. However, these agents are widely used in the management of chronic hepatitis B, and the resistance rate of either agent seems to be lower than lamivudine (12% for adefovir at 3 years,⁹⁵ 1% for entecavir for patients with lamivudine-resistance at 1 year, and 9% at 2 years).⁹⁶ In general, entecavir is preferred because of its high efficacy and low resistance rate. Interferon- α should be avoided in view of the bone marrow suppressive effect and the risk of hepatitis flares.²⁷

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Figure 2 Proposed practical algorithm for the prevention of HBV reactivation in patients with cancer undergoing chemotherapy. Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem cell transplantation; LFT, liver function test.

Unsolved Issues and Future Directions

To date, most studies have compared the effect of prophylactic antiviral therapy against historical controls. Recommendations are based on limited evidence. A lack of prospective, randomized, controlled trials, uncontrolled observational studies, and different definitions of HBV reactivation have prevented a clear understanding of the role of prophylactic antiviral therapy. Unsolved issues include the optimal antiviral agent with higher potency and less resistance, how to monitor patients for reactivation, and when to stop prophylaxis. Prophylactic strategies in patients with resolved HBV and those treated with molecular targeted chemotherapeutic agents also must be elucidated.

Further randomized controlled studies of prophylaxis versus no prophylaxis in breast cancer or lymphoma do not seem to be necessary. Prospective clinical trials regarding different approaches to prophylaxis are warranted. For example, valuable information can be obtained through prospective clinical trials com-

paring the efficacy of lamivudine versus other antiviral agents, such as entecavir, adefovir, and tenofovir, or clinical trials evaluating discontinuation of prophylaxis at 3 or 6 months versus 12 months.

On the research side, a more comprehensive understanding of pathogenesis and identification of viral or host determinants of HBV reactivation enables improved management of HBV reactivation.²⁹

Conclusions

HBV reactivation is a serious clinical problem for HBV carriers undergoing chemotherapy. Screening for HBV is required before chemotherapy, and prophylactic antiviral therapy can reduce not only the incidence of HBV reactivation but also HBV-related morbidity and mortality. Physicians should be aware of this potentially life-threatening but preventable complication, and closely monitor HBV carriers undergoing chemotherapy.

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