World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i7.954

World J Hepatol 2015 May 8; 7(7): 954-967
ISSN 1948-5182 (online)

REVIEW

Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure

Venessa Pattullo

Venessa Pattullo, Department of Gastroenterology, Royal North Shore Hospital, St Leonards NSW 2065, Sydney, Australia
Venessa Pattullo, Sydney Medical School, University of Sydney, Sydney NSW 2006, Australia
Author contributions: Pattullo V solely contributed to this manuscript.
Conflict-of-interest: Venessa Pattullo has received fees for serving as a speaker from Janssen, Merck-Sharpe Dohme and Gilead within the last 5 years (content approved by independent steering committees). There are no other potential conflicts of interest to report.

Correspondence to: Dr. Venessa Pattullo, MBBS, FRACP, PhD, Department of Gastroenterology, Royal North Shore Hospital, 4B Acute Services Building, St Leonards NSW 2065, Sydney, Australia. venessa.pattullo@sydney.edu.au
Telephone: +61-2-94632450
Fax: +61-2-94632041
Received: December 2, 2014
Peer-review started: December 4, 2014
First decision: January 8, 2015
Revised: January 31, 2015
Accepted: February 10, 2015
Article in press: February 12, 2015
Published online: May 8, 2015

Abstract

Due to the inherent relationship between the immune system and the hepatitis B virus (HBV) in exposed and infected individuals, immunomodulation associated with the treatment of solid tumours, haematological malignancies and inflammatory disorders has been linked to HBV reactivation (HBVr). Reactivation of HBV infection in the setting of chemotherapy and immunosuppression may lead to fulminant liver failure and death, but there is a cumulative body of evidence that these are potentially preventable adverse outcomes. As chronic hepatitis B is largely asymptomatic but also endemic worldwide, clinicians caring for patients requiring chemotherapy or immunosuppression need to be vigilant of the potential for HBVr in susceptible individuals. Serological screening and prophylactic and pre-emptive antiviral treatment with a nucleos(t)ide analogue should be considered in appropriate settings. Hepatitis B prevalence is examined in this review article, as are the risks of HBVr in patients receiving chemo- and immunosuppressive therapy. Recommendations regarding screening, monitoring and the role of antiviral prophylaxis are outlined with reference to current international associations' guidelines and the best available evidence to date.

Key words: Immunosuppression; Hepatitis B; Hepatitis B virus reactivation; Prophylaxis; Lamivudine; Chemotherapy; Entecavir; Tenofovir; Rituximab

Core tip: Hepatitis B virus reactivation is a potentially fatal but preventable complication of chemotherapy and immunosuppression. Both chronically infected [hepatitis B surface antigen (HBsAg) positive] and previously exposed (HBsAg negative/anti-HBc positive) patients are susceptible, the risk observed to be strongly associated with the potency of the immunosuppressive drug regime and the baseline virological status. The knowledge gaps that require further investigation in the optimal management of this phenomenon are discussed in this review. Recommendations regarding screening, monitoring and the role of antiviral prophylaxis are outlined with reference to current international associations' guidelines and the best available evidence to date.

Pattullo V. Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure. *World J Hepatol* 2015; 7(7): 954-967 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i7/954.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i7.954

HEPATITIS B EPIDEMIOLOGY

It is estimated that 2 billion people have been infected with hepatitis B worldwide; of these, 350 million of these are chronically infected [chronic hepatitis B (CHB)][1]. Seventy-five percent of the chronically infected reside in the Asia-Pacific region, where the disease is endemic[2,3]. Across the globe, northern, western, and central Europe, North America and Australia have the lowest prevalence of chronic hepatitis B virus (HBV) infection [hepatitis B surface antigen (HBsAg) positive 0.2%-0.5%] and HBV exposure (HBsAg negative but anti-HBc positive 4%-6%); Eastern Europe, the Mediterranean, Russia, Southwest Asia, Central and South America have higher rates (2%-7% chronically infected and 20%-55% exposed) and the highest rates are documented in China, Southeast Asia and tropical Africa (8%-20% chronically infected and 70%-95% exposed)[1]. The Centre for Disease Control (CDC) advises the high-risk groups in the general population (Table 1) who should be screened and managed for chronic HBV infection[4].

HBV INFECTION AND THE IMMUNE SYSTEM

HBsAg positive patients

Chronic HBV infection is characterised by the interaction between the virus, the immune system and the liver itself. This interaction is one that may change spontaneously over time, resulting in the 4 phases of CHB infection [the Hepatitis B e-antigen (HBeAg) positive phases of immune tolerance and immune clearance; the HBeAg negative phases of immune control and immune escape] and the corresponding hepatic consequences[5]. This interaction between virus and host may also be disrupted by any drug-induced modulation of the immune system resulting in HBV reactivation (HBVr), which has the potential to cause significant liver injury.

The liver injury that occurs as a result of a HBVr may arise from two mechanisms[6]. Loss of immune control of the virus during chemo- or immunosuppressive therapy may result in uncontrolled viral replication, with rapid rises in HBV-associated proteins causing overwhelming direct cytolytic destruction of hepatocytes. Alternatively, after cessation of chemotherapy, reconstitution of the immune system may cause severe immune-mediated injury to infected hepatocytes. The exaggerated immune response against hepatocytes expressing hepatitis B viral proteins may cause overwhelming necrosis of liver cells. The reactivation may be delayed, occuring as late as six months after the cessation of chemotherapy. In the case of certain treatment regimens (*e.g.*, rituximab due to prolonged immunosuppression and immune reconstitution phases) reactivation can occur as late as 12 mo post-treatment[7,8]. HBVr presents clinically as a spectrum of asymptomatic biochemical hepatitis through to the more concerning acute symptomatic hepatitis with the potential for liver failure and death[9].

HBsAg negative, anti-HBc positive patients

Individuals known to have CHB (HBsAg positive) may spontaneously lose HBsAg at an annual rate of 0.5%; this is defined as "spontaneous clearance"[10]. Alternatively, patients may have serological evidence of past HBV exposure, both scenarios leading to an HBsAg negative/anti-HBc positive state. These patients by far outnumber those with CHB across the globe[1]. The HBV may persist in hepatocytes and other tissues in the form of covalently closed circular DNA. Although the HBV DNA may not be detectable in serum, they remain at risk of HBVr in the setting of chemo- or immunosuppressive therapy, and the clinical adverse outcomes as described above[11,12].

The significance of anti-HBs

Anti-HBs antibodies may develop in HBsAg negative/anti-HBc positive individuals indicating the development of natural immunity or in anti-HBc negative individuals who have been immunised against HBV. There is limited evidence to date that the presence of anti-HBs protects against HBVr. In one small study of 29 lymphoma patients, no patient (0/10) with an anti-HBs titre of > 100 IU/mL experienced HBVr, and lower anti-HBs titre was independently associated with HBVr[13]. In patients receiving haematopoetic stem cell transplantation, the donor anti-HBs titre was associated with a decreased risk of HBVr[14]. These findings are yet to be validated. Until then, management decisions on the prophylaxis of HBVr cannot be made on the basis of the presence or titre of anti-HBs.

DEFINITIONS OF HBVr AND ASSOCIATED CLINICAL ENDPOINTS

HBVr has been variably defined across the existing studies examining this phenomenon. The HBV DNA assays used have varied in their lower limits of detection, potentially underestimating the prevalence of HBVr and delaying the time point at which HBVr may be first detected thereby limiting the ability to directly compare the results across studies. "Hepatitis" has been variably reported as alanine aminotransferase (ALT) elevation above upper limit of normal, or by "fold" increases from baseline; whether the hepatitis is symptomatic or asymptomatic is inconsistently documented. Suggested definitions for HBVr are listed beneath, however a consensus is yet to be reached for

Table 1 Populations at high risk for hepatitis B virus infection that should be screened[4]

Individuals born in areas of high (≥ 8%) or intermediate prevalence (2%-7%) for HBV (HBsAg positive) including immigrants and adopted children
Asia, Africa, South Pacific Islands: All countries
Middle East (except Cyprus and Israel)
Eastern Europe: All countries except Hungary
European Mediterranean: Malta and Spain
The Arctic (indigenous populations of Alaska, Canada, and Greenland)
South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru
Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos
Central America: Guatemala and Honduras
Other groups recommended for screening
United States born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (8%)
Household and sexual contacts of HBsAg-positive persons
Persons who have ever injected drugs
Persons with multiple sexual partners or history of sexually transmitted disease
Men who have sex with men
Inmates of correctional facilities
Individuals with chronically elevated ALT or AST
Individuals infected with HCV or HIV
Patients undergoing renal dialysis
All pregnant women
Persons needing immunosuppressive therapy

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HIV: Human immunodeficiency virus.

the purposes of future studies.

In HBsAg positive patients: Detectable HBV DNA in individual who previously had undetectable HBV DNA by highly sensitive assay (lower limit of detection < 20 IU/mL); ≥ 1 log rise in HBV DNA in individual who previously had a detectable HBV DNA[15]; biochemical hepatitis (ALT flare): ≥ 3 fold rise in ALT from baseline levels exceeding the reference range or an absolute ALT ≥ 100 IU/mL[15], preceded by a rise in HBV DNA.

Consensus is needed as to a grading of the severity of biochemical hepatitis and associated clinical symptoms for the purposes of reporting in future studies. A 5-point grading system was proposed at a recent single topic conference[16]: (1) Without change in ALT level (silent); (2) Increased ALT level without jaundice (mild); (3) Increased ALT level and concomitant jaundice (moderate); (4) Jaundice and signs of liver failure (severe); and (5) Fatal.

In HBsAg negative, anti-HBc positive patients: Sero-reversion (or reverse seroconversion) is the redevelopment hepatitis B surface antigenemia, HBV DNA viremia with or without hepatitis as a result of reactivation of "occult" infection triggered by chemotherapy or immunosuppression[17].

Clinical endpoints associated with the virological and biochemical changes: Jaundice, liver failure and death.

Another important clinical outcome (and relevant endpoint for future studies) is the interruption of chemo- or immunosuppressive therapy, which may be indicated upon the occurrence of HBVr. In a study of 41 patients with breast cancer, HBVr was diagnosed in 17 (41%), and treatment interruption occurred in 71% of these cases (compared with only 33% of those that did not experience HBVr, $P = 0.019$)[18]. Treatment interruption has the potential to increase morbidity and mortality associated with the underlying malignancy or disease process. Due to a lack of reporting of the occurrence of treatment interruption and the long-term outcomes of cancer- or disease-related morbidity and mortality in the majority of studies of HBVr, the impact of treatment interruption due to HBVr across diseases is not clear and requires further evaluation.

THE MAGNITUDE OF THE RISK OF HBVr

Clinically significant reactivations of HBV have been documented in both cancer and non-cancer patients receiving chemo- or immunomodulating pharmacotherapy. The majority of the studies reporting the rates of HBVr are case reports or small case series using variable definitions of HBVr, hence leading to a broad range of prevalences cited.

Reactivation of HBV has been reported in patients treated for lymphoma, other haematological malignancies and in the setting of haematopoetic stem cell transplant[14,19-22]. The prevalence of CHB in patients with lymphoma has been reported as high as 26%[15]. HBVr can occur in 38%-73% of HBsAg positive patients being treated for lymphoma, the higher HBVr rates seen in patients being treated with chemotherapy regimes including high dose corticosteroids[9,23,24]. Patients who receive a bone marrow transplant (BMT) or haematopoetic stem cell transplant (HSCT) for haematological malignancy are a special population that experience prolonged immunosuppression related to the conditioning chemotherapy leading up to the transplant, post-transplant immunosuppressive therapy as well as a potentially protracted immunodeficient state while engraftment occurs. Fatal HBVr has been observed in HBsAg positive patients, as well as HBsAg negative/anti-HBc positive patients[25,26]. In a multicentre retrospective study of patients receiving both autologous and allogeneic stem cell transplantation, the rates of HBVr at 2 years post-transplant were 66% and 81% respectively; the majority of the reactivations occurred within the first 12 mo post-transplant[27].

Therapy for solid tumours including breast, nasopharyngeal and hepatocellular cancer (the latter in the setting of either systemic chemotherapy or trans-arterial chemoembolisation) has also been associated with HBVr[28-36]. Amongst a cohort of oncology patients with solid tumours, CHB was documented in 12% of patients[15]. These investigators observed that approximately 20% of

Table 2 Immunosuppressive drug classes and corresponding risk estimates of hepatitis B virus reactivation[63,80]

Drug class	Drug	Risk estimate of HBVr for HBsAg positive	Risk estimate of HBVr for HBsAg negative/anti-HBc positive
B-cell depleting agents	Rituximab (anti-CD20)	High (30%-60%)	High (> 10%)
	Ofatumumab (anti-CD20)		
Anthracycline derivatives	Doxorubicin	High (15%-30%)	High (> 10%)
	Epirubicin		
TNF-α inhibitors	Infliximab	Moderate (1%-10%)	Moderate (1%)
	Etanercept		
	Adalimumab		
Cytokine inhibitors and integrin inhibitors	Abatacept (anti-CD80, -86)	Moderate (1%-10%)	Moderate (1%)
	Ustekinumab (anti-IL-12, -23)		
	Natalizumab (binds α4-integrin)		
	Vedolizumab [binds integrin α4β7 (LPAM-1)]		
Tyrosine kinase inhibitors	Imantinib	Moderate (1%-10%)	Moderate (1%)
	Nilotinib		
Corticosteroids	High dose, *e.g.*, prednisone ⩾ 20 mg for ⩾ 4 wk	High (> 10%)	NA
	Moderate dose, *e.g.*, prednisone < 20 mg for ⩾ 4 wk	Moderate (1%-10%)	Moderate (1%-10%)
	Low dose, *e.g.*, prednisone for < 1 wk	Low (< 1%)	Low (<< 1%)
	Intra-articular corticosteroids	Low (< 1%)	Low (<< 1%)
Traditional immunosuppression	Azathioprine	Low (< 1%)	Low (<< 1%)
	6-mercaptopurine		
	Methotrexate		

TNF: Tumour necrosis factor; IL: Interleukin; LPAM: Lymphocyte Peyer's patch adhesion molecule; NA: Not available; HBVr: Hepatitis B reactivation; HBsAg: Hepatitis B surface antigen.

CHB patients receiving chemotherapy for their malignancy experienced HBVr[15]. Forty-one percent of breast cancer patients positive for HBsAg have been reported to experience HBVr[18].

HBVr has been reported in patients receiving immunosuppression for inflammatory bowel disease[37,38], rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis)[39-44], dermatological disorders (psoriasis)[45], autoimmune disorders[46,47] and in those following solid organ transplantation (*e.g.*, renal and liver)[48-52].

FACTORS ASSOCIATED WITH HBVr

Elucidating the risk factors for HBVr amongst those receiving chemo- or immunosuppressive therapy may help to identify cases that should receive antiviral prophylaxis. Patient-specific risk factors associated with reactivation include younger age, male gender and the type of treatment regimens prescribed[9,53,54].

Virological and serological status

Detectable HBV DNA, HBsAg, HBeAg and anti-HBc are important virological and serological markers strongly associated with HBVr[10-12,17,55]. High HBV DNA is the strongest of these risk factors, and HBsAg positive patients are up to 8 times more likely to experience HBVr than HBsAg negative/anti-HBc positive patients[30,56,57]. Amongst HBsAg positive patients, HBeAg positive patients have been observed to be more likely to experience HBVr than HBeAg negative patients[56]. The HBV genotype appears to be significant in that HBV genotypes C and B (prevalent in East Asia but rare in Caucasians) correlate with HBVr[9,58,59]. The latter observations may simply be a reflection of the prevalent genotypes in these geographical regions and requires further investigation.

Mutations of the HBsAg may confer risk of HBVr[60]. In a recent study of 93 patients with CHB (29 of whom developed HBVr) the HBsAg genetic features were analysed. HBsAg-mutations localised in immune-active HBsAg regions were observed in 76% patients who experienced HBVr (*vs* 3.1% controls, $P < 0.001$). Of the 13 HBsAg-mutations found in these patients, 8 are known to block HBsAg-recognition by the humoral immune pathway and the remaining 5 mutations were identified within in Class-Ⅰ/Ⅱ-restricted T-cell epitopes (potentially influencing T-cell mediated responses to HBV-escape)[60]. These observations suggest that patients infected with HBV expressing such HBsAg-mutations may be more able to overcome the normal immune response, thereby being more at risk of HBVr with chemotherapy. The clinical application of these findings is yet to be determined.

Chemotherapy/Immunosuppression drug class

The pharmacotherapy used to manage malignant and inflammatory conditions is rapidly evolving with new and targeted agents being developed. Several of these newer agents have the potential to disrupt the control that the immune system has over any underlying HBV exposure or chronic infection. Clinical evidence of HBVr with these agents has subsequently been apparent in case reports and case series. A list of the drug classes listed from most potent to least potent of the agents appears in Table 2.

The B-cell depleting agents appear to be the most potent immunosuppressants (and thereby associated with the highest risk of HBVr). Rituximab and ofatumumab are two B-cell depleting agents predominantly

used to treat haematological malignancy, however rituximab has been used for non-malignant autoimmune and neurological diseases[61,62]. Both HBsAg positive and HBsAg negative/anti-HBc positive patients who receive these agents appear to be susceptible to HBVr. The rate of HBVr with these agents in HBsAg negative/anti-HBc positive patients has been reported at 16.9%, and seroreversion rate of 20%-40%[63-65]. HBVr has occurred up to 12 mo after cessation of B-cell depleting drugs (and in a small number of cases delayed beyond 12 mo) indicating the potency of the immunosuppressive effect of this drug class and the prolonged immune reconstitution phase. A study of 63 HBsAg negative/anti-HBc positive patients with haematological malignancy who received rituximab without antiviral prophylaxis has been reported[20]. At 2 years, 41.5% had experienced HBVr which occurred at a median of 23 (range 4-100) wk after rituximab treatment[20]. These observations would indicate that any monitoring or antiviral prophylaxis prescribed to these patients may require longer duration than other classes of immunosuppressive drugs.

Tumor necrosis factor (TNF)-alpha inhibitor agents include infliximab, etanercept and adalimumab, which have been used in the management of inflammatory bowel disease, rheumatological disease and psoriasis (amongst other disorders). All 3 drugs have been associated with HBVr[66]. The absolute risk of HBVr with these agents is not clear owing to the heterogeneity of the cases and cohorts reported. A larger study of 257 cases exposed to anti-TNF agents for a variety of indications reported a HBVr rate of 39% in HBsAg positive patients and 7 fold lower rate of HBVr in anti-HBc positive patients[67].

Cytokine and integrin inhibitors, by virtue of their interaction with the immune system, have also been associated with HBVr. Drugs of this class and their target molecules are listed in Table 2. Evidence of role of these drugs in HBVr exists largely as case reports and small case series [54,55,68].

Tyrosine kinase inhibitors including imantinib and nilotinib are used to treat chronic myeloid leukaemia and gastrointestinal stromal tumours. Evidence of HBVr is limited, again, to case reports and small case series[69-74].

Corticosteroids are the most longstanding and hence most commonly used of the immunosuppressants across all the aforementioned disease processes. In addition to their effect on T-cell function, corticosteroids directly enhance HBV replication through their interaction with the HBV glucocorticoid responsive element (a transcriptional regulatory element)[75]. Although steroids are administered at a range of dosages and durations for a variety of indications, it has been observed that a 4-wk course of prednisone has been associated with HBVr in the post-withdrawal (immune reconstitution) phase and worsened liver histology[76]. Chronic steroid use in the setting of chronic airways disease is associated with HBVr in 11.1% of those treated with oral steroids and 3.2% of those treated with inhaled steroids[77]. In the aforementioned study (including 198 patients with asthma or chronic obstructive pulmonary disease) continuous oral corticosteroid therapy (> 3 mo) and high-dose (defined as > 20 mg prednisone/day) were associated with HBVr with OR of 5.7 and 4.9 respectively, when compared with HBVr in those receiving inhaled corticosteroids[77]. Low dose, short term (< 2 wk) administration of oral (systemic) corticosteroids, intraarticular injection and topical therapies have not been associated with HBVr. These data taken together indicate that corticosteroids have the potential to induce HBVr, but that the risk varies according to the dose, duration and route of administration of the drug.

"Traditional" immunomodulating drugs such as azathioprine, 6-mercaptopurine and methotrexate appear to have the lowest potential for HBVr. There are no documented cases of HBVr with the use of azathioprine or 6-mercaptopurine monotherapy. Cases of HBVr have been reported with methotrexate, however corticosteroids or other immunomodulators were co-administered in most instances, compounding the risk of HBVr[78,79].

The risk of HBVr associated with each of the drug classes administered to HBsAg positive or HBsAg negative/anti-HBc positive patients has been estimated by the American Gastroenterological Association (AGA) based on a thorough systematic review of the existing literature[63,80]. This risk stratification is summarised in Table 2. The risk of HBVr may be stratified to high (> 10% risk of HBVr), moderate (1%-10%) and low (< 1%). The current AGA recommendations are based on the risk of HBVr according to the combination of serological markers of HBV and the chemotherapy/immunosuppression regimen prescribed and, to date, are the most detailed and specific recommendations with regard to the patient risk groups in whom antiviral prophylaxis should be considered[63,80].

Hepatitis B and delta co-infection

To date, only a single case report of hepatitis delta (HDV) reactivation in association with HBVr exists[81]. This patient was co-infected with hepatitis C (HCV RNA positive), HBV (HBsAg positive, HBV DNA undetectable at baseline) and had evidence of cleared HDV infection (anti-HDV positive). A rituximab-CHEOP regime was prescribed to treat lymphoma; HBV DNA became detectable during chemotherapy. Subsequently, 15 mo after chemotherapy, HDV RNA was detected at a level of 77.6 million copies/mL. The patient was managed successfully with lamivudine, which was in turn switched to emtricitabine/tenofovir. Given the singularity of this report, there is no real evidence base to guide the management of HBV-HDV co-infection in this setting and patients should be managed according to their HBV status.

MANAGEMENT OF HBVr

HBVr occurring during chemo- or immunosuppressive therapy, if detected, may be an indication to delay

or cease therapy. Withholding chemotherapy may halt or reduce the rate of HBV replication potentially abrogating the HBVr. As discussed, in the absence of antiviral prophylaxis, HBVr may also occur in the post-chemotherapy immune reconstitution phase.

The role of antiviral therapy once HBVr is already established has been investigated by several groups. In a prospective study of patients treated for non-Hodgkin's lymphoma, lamivudine therapy started when ALT elevation was detected did not change the natural course of HBVr; 2 patients in this cohort died despite lamivudine use at the onset of HBVr[8]. Numerous case reports and series describe death due to liver failure despite the introduction of lamivudine at the onset of HBVr[82-86]. Only a few cases of successful treatment of HBVr with entecavir have been published[87-89]. Despite the paucity of data regarding the efficacy of entecavir to treat established HBVr (and no data to date regarding tenofovir), the ability of these drugs to rapidly reduce HBV DNA make them attractive alternatives to lamivudine in patients who experience HBVr to potentially abrogate the risk of liver failure and mortality. Data on the efficacy and cost-effectiveness of these approaches to management are needed.

PREVENTION OF HBVr

Given the poor outcomes associated with reactionary treatment of HBVr (*i.e.,* antiviral treatment once HBVr is already established), strong consideration must be given to the role of antiviral prophylaxis in at-risk patients who will receive chemo- or immunosuppressive therapy.

A systematic review of studies examining the role of antiviral prophylaxis in chemotherapy patients concluded that lamivudine prophylaxis (*vs* no prophylaxis) is associated with a relative risk of 0.0-0.21 for HBVr and 0.0-0.2 for death attributable to HBV[90]. Liver failure was not observed in any patient who received lamivudine prophylaxis[90]. In line with these observations, a subsequent systematic review reported that patients given lamivudine prophylaxis during chemotherapy showed an 87% decrease in HBVr compared to patients not given prophylaxis[91]. It is noteworthy to mention that the number needed to treat to prevent one reactivation was just 3 patients[91]. Treatment delay and early cessation of chemotherapy due to HBVr were also reduced by 92% in those who received lamivudine[91].

Most recently, a systematic review and metanalysis of 5 randomised controlled trials comparing antiviral prophylaxis to treatment at the onset of HBVr has been published[63]. Lamivudine was used in 4 studies and entecavir was used in 1 study[8,92-95]. The overall risk ratio (RR) favoured the prophylactic use of antivirals over no antivirals [RR = 0.13 (0.06-0.30)][63]. Antiviral prophylaxis was also associated with a significant risk reduction of hepatitis flare [RR = 0.16 (0.06-0.42)][63].

Owing to the fewer occurrences and lower severity of HBVrs, the use of lamivudine prophylaxis has been deemed to be a cost-effective intervention. The cancer death rate in patients who receive prophylaxis is also reduced, presumably due to the reduced rate of chemotherapy interruption or curtailment[96]. The cost-effectiveness of entecavir and tenofovir have not, as yet, been evaluated.

The duration of antiviral prophylaxis remains under debate. As discussed, delayed HBVr has been observed in patients 6-12 mo after completion of chemotherapy (in the absence of antiviral prophylaxis) in both HBsAg positive and HBsAg negative/anti-HBc positive patients, and also when the antiviral prophylaxis has been curtailed to 2 mo post-completion of antiviral therapy[8]. The duration of risk of HBVr appears to be strongly related to the potency of treatment regime, again mentioning that patients who have received B-cell depleting agents appear to be susceptible to delayed HBVr (up to 12 mo post-treatment and beyond)[20]. Hence, antiviral prophylaxis may be required for at least 6 mo after cessation of chemo- or immunosuppressive therapy and for at least 12 mo for those receiving B-cell depleting agents; subsequent monitoring for delayed HBVr after cessation of antiviral prophylaxis is essential.

Mention must be made of the role of antiviral prophylaxis in recipients of bone marrow or haematopoetic stem cell transplants. Both lamivudine and entecavir have been used with the aim of preventing HBVr in these cases[97-101]. The optimal timing of withdrawal of antiviral prophylaxis, however, remains unclear. HBVr has been observed as early as 12 wk post-discontinuation of lamivudine in the bone marrow transplant setting[98]. In a study of 16 patients who received lamivudine for a median of 73 wk (range 19-153) after stem cell transplantation, the cumulative rate of HBVr at 30 mo follow-up was 20%; 63% of the patients developed documented lamivudine resistance and one patient had virological breakthrough during the study period[99]. HBVr has been diagnosed as late as 4 years after transplantation in a patient who was anti-HBs positive at baseline[102]. It would appear that BMT/HSCT recipients are potentially at risk of HBVr for years after the transplant and consideration must be given to whether these patients require antiviral therapy long term. If therapy were to continue long term, then consideration must be given to the risk of lamivudine resistance, and hence entecavir and tenofovir may be more suitable choices for antiviral prophylaxis due to their high barrier for drug resistance. The current evidence base to address these issues is weak, and further study is required. Of the major international associations' guidelines, only the European Association for the Study of Liver Disease (EASL) guidelines (2009) provide a recommendation for this patient population: that nucleos(t)ide analogue prophylaxis is recommended for anti-HBc positive patients receiving bone marrow or stem cell transplantation (grade of recommendation C2); a duration of therapy is not specified[103].

Based on the available data, prophylactic antiviral

therapy in the appropriate candidates appears to reduce the risk of HBVr and morbidity. Further studies are required to determine the impact on overall and cancer-related survival and the cost effectiveness of the strategies employed (drug choice, duration of therapy).

CHOICE OF ANTIVIRAL AGENT

The drugs currently available for the management of chronic hepatitis B include lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir disoproxil fumarate. By far, the largest body of literature on the prevention of HBVr examines the role of lamivudine, the first of these drugs to be available. The downside of lamivudine use is the high rate of drug resistance (and potential for virological breakthrough or relapse) reported to be 20% within the first 12 mo of use. Fatal HBVr despite lamivudine prophylaxis owing to the development of the M204 drug resistance mutation has been reported in a patient who received R-CHOP for lymphoma[104]. Lamivudine may have a role where total chemotherapy and post-chemotherapy follow-up duration spans less than 12 mo (thereby reducing risk of drug resistance and virological breakthrough), the HBV DNA is undetectable at baseline and the patient is not receiving any of the "high risk" treatment regimes. The latter approach requires further evaluation, but may be an attractive strategy, *e.g.*, in countries with high prevalences of HBV where the cost of the more potent antivirals may be prohibitive.

With substantially lower antiviral resistance rates than lamivudine, entecavir and tenofovir may be a more suitable first line for HBV DNA suppression in those with high pre-chemotherapy HBV DNA levels in order to mitigate HBVr. There are five studies to date comparing entecavir to lamivudine or no prophylaxis in patients with haematological malignancy or lymphoma alone[92,105-108]. Lower rates of HBVr are generally observed with the use of entecavir in these studies, however these studies vary in their design (ranging from retrospective audit to randomised-controlled study) and hence the strength of their findings. In the single randomised controlled study (published in abstract form), 61 patients who received entecavir prophylaxis were compared to 60 patients who received lamivudine[92]. Entecavir was associated with a relative risk reduction of 0.22 (0.08-0.61) for HBVr and had significantly fewer chemotherapy interruptions (1.6% *vs* 18.3%)[92]. Further data is awaited, as are studies on the role of tenofovir in this setting, but it is expected that given the limitations of lamivudine, entecavir and tenofovir will have a greater role in the prevention of HBVr in the future.

The data regarding adefovir and telbivudine in the prevention and management of HBVr is limited to the liver transplantation setting and is outside of the scope of discussion of this review. These drugs are not recommended as first line drugs for prophylaxis of HBVr in the context of chemotherapy or immunosuppression.

SCREENING FOR HBV PRIOR TO CHEMOTHERAPY OR IMMUNOSUPPRESSION

Given the risk of HBVr in patients previously exposed or chronically infected with HBV and receiving chemotherapy or immunosuppression, it is essential for clinicians caring for such patients to be aware of this risk and screen for HBV in order to institute appropriate prophylactic therapy or monitoring. Additionally, screening may uncover previously unrecognized chronic hepatitis B infection and subsequently the complications of cirrhosis and hepatocellular cancer. These liver-related complications require long-term and directed management and may influence the management underlying malignancy/disease.

There are several approaches to screening for HBV in this patient population: (1) Screen all patients prior to chemotherapy/immunosuppression[103,109]. This strategy would identify patients who would potentially benefit from: Antiviral prophylaxis; HBV serology and HBV DNA monitoring (without antiviral prophylaxis); Immunisation against HBV; Evaluation for complications of CHB; Contact tracing of family members for CHB and their subsequent management; (2) Screen only patients at risk of HBV according to CDC "high risk" groups (Table 1)[4,110]; and (3) Screen only patients who, if serological testing was positive, would be prescribed antiviral prophylaxis[63,80,111].

Consideration must also be given to the serological test(s) to be used for screening. The approaches to serological screening for HBV include: (1) Test HBsAg, anti-HBc and anti-HBs. Test HBV DNA if HBsAg or anti-HBc are positive (the latter in case of occult HBV infection); (2) Test HBsAg, anti-HBc only. The role of anti-HBs in HBVr is unclear. Furthermore, immunisation against HBV may not be efficacious during immunosuppression. Therefore, one may argue that anti-HBs status may not be relevant prior to chemotherapy; and (3) Test anti-HBc only. If positive, proceed to test for HBsAg and HBV DNA.

There is a paucity of data on the best and most cost-effective approach to screening for HBV in patients at risk of HBVr. Each of the major international associations has made screening recommendations (summarised in Table 3), which vary across the associations. The most recent and complete of the systematic reviews performed (as at 2014) has estimated risk of HBVr according to specific chemotherapy/immunosuppressive regime, and hence recommends HBV serological screening in patients with moderate to high risk[63,80]. The clinical decision on who and how to screen will likely be influenced by the characteristics of the population being managed and the resources available to the individual, the institution

Table 3 Comparison of International Associations' guidelines on the management of hepatitis B virus in the setting of chemotherapy and immunosuppression

Association guidelines	HBV screening population	Screening test	Antiviral prophylaxis		Antiviral drug recommended for prophylaxis	Monitoring in untreated anti-HBc + ve patients
			HBsAg + ve, anti-HBc + ve	HBsAg - ve, Anti-HBc + ve		
American Gastroenterological Association 2014[63,80]	High risk of HBVr (> 10%)	HBsAg and anti-HBc; HBV DNA if serology + ve	Yes (B1)	Yes (B1) if taking:	Drug with high barrier to resistance is favoured over lamivudine (B2)	No recommendation (knowledge gap)
	B-cell depleting agents		Continue until at least 6 mo after completion of chemotherapy	B-cell depleting agents		
	Anthracycline derivatives High dose corticosteroids (≥ 20 mg prednisone for ≥ 4 wk)			Anthracycline derivatives Continue until at least 12 mo after completion of chemotherapy for B-cell depleting agents		
	Moderate risk of HBVr (1%-10%)	HBsAg and anti-HBc; HBV DNA if serology + ve	Yes (B2)	Yes (B2) if taking	Drug with high barrier to resistance is favoured over lamivudine (B2)	No recommendation (knowledge gap)
	TNF-α inhibitors		Continue until at least 6 mo after completion of chemotherapy	TNF-α inhibitors		
	Cytokine or integrin inhibitors			Cytokine or Integrin inhibitors		
	Tyrosine kinase inhibitors High dose corticosteroids (≥ 20 mg prednisone for ≥ 4 wk)			Tyrosine kinase inhibitors Continue until at least 6 mo after completion of chemotherapy		
	Low risk of HBVr (< 1%)	Routine screening not recommended	Not recommended (B2)	Not recommended (B2)	Not applicable	No recommendation (knowledge gap)
	Traditional immunosuppression Intra-articular corticosteroids Systemic corticosteroids for < 1 wk	Screen for HBV as per CDC guidelines[4]; manage accordingly				
American Association for the Study of Liver Disease 2009[110]	Anyone at high risk of HBV infection; Table 1 (Ⅱ-3)	HBsAg and anti-HBc	Yes (regardless of HBV DNA level)	No recommendation (knowledge gap)	Lamivudine (Ⅰ) or telbivudine (Ⅲ) if the anticipated treatment duration is short (< 12 mo) and baseline HBV DNA is not detectable	Monitoring recommended; no specific test/frequency provided
			Maintain for 6 mo completion of chemotherapy (Ⅲ)		Tenofovir or entecavir if anticipated treatment duration > 12 mo (Ⅲ)	
			If baseline HBV DNA > 2000 IU/mL, continue antiviral until endpoints as per immunocompetent patients (Ⅲ)			

European Association for the Study of Liver Disease 2012[103]	All candidates for chemo- and immunosuppressive therapy (A1)	HBsAg and anti-HBc; HBV DNA if serology + ve	Yes (A1) Regardless of HBV DNA level Continue until 12 mo after cessation of chemotherapy	Yes if: HBV DNA detectable Taking rituximab (C2) Bone marrow or stem cell transplantation (C2) Treat as per HBsAg + ve No if: HBV DNA undetectable; monitor	Lamivudine if HBV DNA < 2000 IU/mL and the treatment duration is short/finite (B1) Entecavir or tenofovir if HBV DNA is high, lengthy or repeated cycles of immunosuppression (C1)	ALT and HBV DNA every 1-3 mo Treat upon evidence of HBVr (C1)
Asian-Pacific Association for the Study of Liver Disease 2012[109]	All patients prior to receiving immunosuppression or chemotherapy	HBsAg (IVA) Test anti-HBc if patient due to receive biological agent	Yes HBVr prophylaxis with lamivudine; Continue until 6 mo after end of chemotherapy (ⅠA) Alternatively use entecavir or tenofovir (ⅢA) Continue HBV treatment if clinically indicated (ⅠA)	No; monitor		HBV DNA should be closely monitored and treated with nucleos(t)ide analogue when needed (IVA)
American Society of Clinical Oncology Provisional Clinical Opinion 2010[111]	Advise against routine serological screening. Screen those with High risk of HBV exposure; evidence of liver disease Therapeutic regimen with high risk of HBVr including all patients undergoing rituximab therapy Haematopoetic stem cell transplant	HBsAg; anti-HBc if receiving rituximab	Consider role of antiviral therapy Do not delay chemotherapy	No specific recommendation provided	No specific recommendation provided	No specific recommendation provided

The grade of recommendation and/or level of evidence have been noted where available. AGA and EASL guidelines: evidence grade A: High quality; B: Moderate quality; C: Low quality. Recommendation grade 1: Strong; 2: Weak. Ⅰ: Randomised controlled trials; AASLD guidelines: Ⅱ-1: Non-randomised controlled trials; Ⅱ-2: Cohort or case-control studies; Ⅱ-3: Case series; Ⅲ: Expert opinion. APASL guidelines: Quality of evidence ranked from Ⅰ (highest) to Ⅴ (lowest); strength of recommendations ranked A (strongest) to D (weakest). HBV: Hepatitis B virus; HBVr: Hepatitis B virus reactivation; CDC: The Centre for Disease Control; + ve: Positive; - ve: Negative; ALT: Alanine aminotransferase.

and nation to fund the serological testing and manage positive results. Studies evaluating the efficacy and cost-effectiveness of the various screening strategies as relevant to the main global regions are needed.

MONITORING IN ANTI-HBC POSITIVE PATIENTS WHO DO NOT RECEIVE ANTIVIRAL PROPHYLAXIS

The data presented in this review thus far indicate that not all HBsAg negative/anti-HBc positive patients will benefit from antiviral prophylaxis, *e.g.*, patients with undetectable HBV DNA who are prescribed lower potency or limited duration immunosuppressive drug regimes. In those who do not receive antiviral prophylaxis, monitoring for features of HBVr is intuitive, however there is a paucity of data as to how this monitoring should be carried out. There is a general consensus from the international associations that some form of monitoring is required. The EASL recommends ALT and HBV DNA testing every 1-3 mo and treatment upon any evidence of HBVr, but this is based on relatively weak level of evidence (C1, Table 3). An alternative approach may be to test for HBsAg in HBsAg negative/anti-HBc positive patients to monitor for seroreversion, which may occur prior to detection of HBV DNA or ALT rise. The remainder of the major societies do not make specific recommendations owing to the knowledge gap in this area. Further data is required to determine the method, frequency and duration of monitoring. Similar to issues arising regarding screening for HBV, the monitoring for HBVr in patients who do not receive prophylaxis will be guided by the prevalence of HBV and HBVr, cost-effectiveness as well as the access to testing and follow-up that varies across the globe.

MONITORING AFTER THE CESSATION OF ANTIVIRAL PROPHYLAXIS

Some patients who receive antiviral therapy at the initiation of chemotherapy or immunosuppression may need to remain on antivirals long term if there is underlying chronic liver disease and ongoing treatment criteria are met[103,109,110]. In those who receive antiviral prophylaxis without otherwise meeting ongoing treatment criteria for chronic HBV, once the decision has been made to cease antiviral prophylaxis there is no evidence base to guide how monitoring is best performed. The major associations do not make specific recommendations as to how to perform post-prophylaxis monitoring. Measurement of HBV DNA and ALT every 1-2 mo for 3-6 mo after cessation of lamivudine prophylaxis have been proposed[90], but based the observations of many of the aforementioned studies, these patients should be monitored for at least 12 mo, if not, long-term. Furthermore, relapse of the underlying malignancy requiring resumption of chemotherapy would warrant reinstitution of antiviral prophylaxis and should not be overlooked.

A COMPARISON OF THE INTERNATIONAL GUIDELINES ON THE PREVENTION AND MANAGEMENT OF HBVr

The guidelines of the major international associations for the HBV screening, antiviral prophylaxis and monitoring have been referenced, where relevant, throughout this review and are summarised in Table 3, the most recent being the technical review and guidelines of the American Gastroenterological Association[63,80]. It must be noted that some of these recommendations span back to 2009, and as such more recent data would not have been included when older recommendations were made. The application of these guidelines by the clinician warrants consideration of clinical circumstances, resources available and cost-effectiveness, which are patient and region/nation specific.

CONCLUSION

Clinicians managing patients with malignancy need to be vigilant of the potential for HBVr as a complication of chemotherapy in susceptible cases. Those at risk for HBVr must be screened serologically for the virus according to international guidelines, which are based on the best available evidence. Prophylactic antiviral therapy with lamivudine or other nucleos(t)ide analogue should be instituted prior to the start of chemotherapy. Prevention is better than cure.

REFERENCES

1 **World Health Organisation**. Hepatitis B. [Accessed 28 November 2014]. Available from: URL: http: //www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index1.html

2 **Benson J**, Donohue W. Hepatitis in refugees who settle in Australia. *Aust Fam Physician* 2007; **36**: 719-727 [PMID: 17885706]

3 **Mohamed R**, Desmond P, Suh DJ, Amarapurkar D, Gane E, Guangbi Y, Hou JL, Jafri W, Lai CL, Lee CH, Lee SD, Lim SG, Guan R, Phiet PH, Piratvisuth T, Sollano J, Wu JC. Practical difficulties in the management of hepatitis B in the Asia-Pacific region. *J Gastroenterol Hepatol* 2004; **19**: 958-969 [PMID: 15304110 DOI: 10.1111/j.1440-1746.2004.03420.x]

4 **Weinbaum CM**, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008; **57**: 1-20 [PMID: 18802412]

5 **Pattullo V**, George J. Managing the Patient with Chronic Hepatitis Receiving Chemotherapy. In: Robotin M, Olver I, Girgis A, editors. In consultation: when cancer crosses disciplines A clinician's handbook. Imperial College Press, 2009: 813-832

6 **Suhail M**, Abdel-Hafiz H, Ali A, Fatima K, Damanhouri GA, Azhar E, Chaudhary AG, Qadri I. Potential mechanisms of hepatitis B virus induced liver injury. *World J Gastroenterol* 2014; **20**: 12462-12472 [PMID: 25253946 DOI: 10.3748/wjg.v20.i35.12462]

7 **Dai MS**, Chao TY, Kao WY, Shyu RY, Liu TM. Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. *Ann Hematol* 2004; **83**: 769-774 [PMID: 15338194 DOI: 10.1007/s00277-004-0899-y]

8 **Hsu C**, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, Lin TH, Hsiao HH, Young JH, Chang MC, Liao YM, Li CC, Wu HB,

Tien HF, Chao TY, Liu TW, Cheng AL, Chen PJ. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 2008; **47**: 844-853 [PMID: 18302293 DOI: 10.1002/hep.22106]

9 **Lok AS**, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991; **100**: 182-188 [PMID: 1983820]

10 **Liaw YF**, Sheen IS, Chen TJ, Chu CM, Pao CC. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. *Hepatology* 1991; **13**: 627-631 [PMID: 2010157]

11 **Bréchot C**, Degos F, Lugassy C, Thiers V, Zafrani S, Franco D, Bismuth H, Trépo C, Benhamou JP, Wands J. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. *N Engl J Med* 1985; **312**: 270-276 [PMID: 2981408 DOI: 10.1056/NEJM198501313120503]

12 **Chemin I**, Jeantet D, Kay A, Trépo C. Role of silent hepatitis B virus in chronic hepatitis B surface antigen(-) liver disease. *Antiviral Res* 2001; **52**: 117-123 [PMID: 11672821]

13 **Pei SN**, Ma MC, Wang MC, Kuo CY, Rau KM, Su CY, Chen CH. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. *Ann Hematol* 2012; **91**: 1007-1012 [PMID: 22273839 DOI: 10.1007/s00277-012-1405-6]

14 **Mikulska M**, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, Di Grazia C, Dominietto A, Varaldo R, Ghiso A, Bacigalupo A, Viscoli C. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. *Clin Microbiol Infect* 2014; **20**: O694-O701 [PMID: 24575948 DOI: 10.1111/1469-0691.12611]

15 **Yeo W**, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299-307 [PMID: 11055239 DOI: 10.1002/1096-9071(200011)62:3<299::AID-JMV1>3.0.CO;2-0]

16 **Hoofnagle JH**. Reactivation of hepatitis B: definition and terminology. Proceedings of the Emerging Trends Conference on HBV Reactivation. USA: Crystal City, VA, 2013: 17-20

17 **Wands JR**, Chura CM, Roll FJ, Maddrey WC. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* 1975; **68**: 105-112 [PMID: 1054319]

18 **Yeo W**, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, Zhong S, Johnson PJ. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003; **70**: 553-561 [PMID: 12794717 DOI: 10.1002/jmv.10430]

19 **Pei SN**, Chen CH. Risk and prophylaxis strategy of hepatitis B virus reactivation in patients with lymphoma undergoing chemotherapy with or without rituximab. *Leuk Lymphoma* 2015: 1-8 [PMID: 25248874]

20 **Seto WK**, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014; **32**: 3736-3743 [PMID: 25287829 DOI: 10.1200/jco.2014.56.7081]

21 **Schubert A**, Michel D, Mertens T. Late HBsAg seroreversion of mutated hepatitis B virus after bone marrow transplantation. *BMC Infect Dis* 2013; **13**: 223 [PMID: 23679074 DOI: 10.1186/1471-2334-13-223]

22 **Li J**, Huang B, Li Y, Zheng D, Zhou Z, Liu J. Hepatitis B virus reactivation in patients with multiple myeloma receiving bortezomib-containing regimens followed by autologous stem cell transplant. *Leuk Lymphoma* 2015: 1-8 [PMID: 25098429 DOI: 10.3109/10428194.2014.941833]

23 **Liao CA**, Lee CM, Wu HC, Wang MC, Lu SN, Eng HL. Lamivudine for the treatment of hepatitis B virus reactivation following chemotherapy for non-Hodgkin's lymphoma. *Br J Haematol* 2002; **116**: 166-169 [PMID: 11841412 DOI: 10.1046/j.1365-2141.2002.03239.x]

24 **Cheng AL**, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, Kao WY, Uen WC, Hsu CH, Tien HF, Chao TY, Chen LT, Whang-Peng J. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003; **37**: 1320-1328 [PMID: 12774010 DOI: 10.1053/jhep.2003.50220]

25 **Dhédin N**, Douvin C, Kuentz M, Saint Marc MF, Reman O, Rieux C, Bernaudin F, Norol F, Cordonnier C, Bobin D, Metreau JM, Vernant JP. Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. *Transplantation* 1998; **66**: 616-619 [PMID: 9753342]

26 **Senecal D**, Pichon E, Dubois F, Delain M, Linassier C, Colombat P. Acute hepatitis B after autologous stem cell transplantation in a man previously infected by hepatitis B virus. *Bone Marrow Transplant* 1999; **24**: 1243-1244 [PMID: 10642815 DOI: 10.1038/sj.bmt.1702039]

27 **Locasciulli A**, Bruno B, Alessandrino EP, Meloni G, Arcese W, Bandini G, Cassibba V, Rotoli B, Morra E, Majolino I, Alberti A, Bacigalupo A. Hepatitis reactivation and liver failure in haemopoietic stem cell transplants for hepatitis B virus (HBV)/hepatitis C virus (HCV) positive recipients: a retrospective study by the Italian group for blood and marrow transplantation. *Bone Marrow Transplant* 2003; **31**: 295-300 [PMID: 12621466 DOI: 10.1038/sj.bmt.1703826]

28 **Dai MS**, Wu PF, Lu JJ, Shyu RY, Chao TY. Preemptive use of lamivudine in breast cancer patients carrying hepatitis B virus undergoing cytotoxic chemotherapy: a longitudinal study. *Support Care Cancer* 2004; **12**: 191-196 [PMID: 15074316 DOI: 10.1007/s00520-003-0549-2]

29 **Dai MS**, Wu PF, Shyu RY, Lu JJ, Chao TY. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. *Liver Int* 2004; **24**: 540-546 [PMID: 15566502 DOI: 10.1111/j.1478-3231.2004.0964.x]

30 **Zhong S**, Yeo W, Schroder C, Chan PK, Wong WL, Ho WM, Mo F, Zee B, Johnson PJ. High hepatitis B virus (HBV) DNA viral load is an important risk factor for HBV reactivation in breast cancer patients undergoing cytotoxic chemotherapy. *J Viral Hepat* 2004; **11**: 55-59 [PMID: 14738558 DOI: 10.1046/j.1352-0504.2003.00467.x]

31 **Teplinsky E**, Cheung D, Weisberg I, Jacobs RE, Wolff M, Park J, Friedman K, Muggia F, Jhaveri K. Fatal hepatitis B reactivation due to everolimus in metastatic breast cancer: case report and review of literature. *Breast Cancer Res Treat* 2013; **141**: 167-172 [PMID: 24002736 DOI: 10.1007/s10549-013-2681-0]

32 **Zheng Y**, Zhang S, Tan Grahn HM, Ye C, Gong Z, Zhang Q. Prophylactic Lamivudine to Improve the Outcome of Breast Cancer Patients With HBsAg Positive During Chemotherapy: A Meta-Analysis. *Hepat Mon* 2013; **13**: e6496 [PMID: 23805156 DOI: 10.5812/hepatmon.6496]

33 **Yeo W**, Hui EP, Chan AT, Ho WM, Lam KC, Chan PK, Mok TS, Lee JJ, Mo FK, Johnson PJ. Prevention of hepatitis B virus reactivation in patients with nasopharyngeal carcinoma with lamivudine. *Am J Clin Oncol* 2005; **28**: 379-384 [PMID: 16062080]

34 **Yeo W**, Lam KC, Zee B, Chan PS, Mo FK, Ho WM, Wong WL, Leung TW, Chan AT, Ma B, Mok TS, Johnson PJ. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004; **15**: 1661-1666 [PMID: 15520068]

35 **Lao XM**, Zheng XR, Lin X. Hepatitis B virus reactivation and liver function after chemoembolization for hepatocellular carcinoma: How is it different from systemic chemotherapy? *Asia Pac J Clin Oncol* 2013; **9**: 381-382 [PMID: 24131744 DOI: 10.1111/ajco.12134]

36 **Jang JW**. Hepatitis B virus reactivation in patients with hepato-

cellular carcinoma undergoing anti-cancer therapy. *World J Gastroenterol* 2014; **20**: 7675-7685 [PMID: 24976705 DOI: 10.3748/wjg.v20.i24.7675]
37 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601 DOI: 10.1136/gut.2004.040675]
38 **Gisbert JP**, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 619-633 [PMID: 21416659]
39 **Calabrese LH**, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis* 2006; **65**: 983-989 [PMID: 16627542 DOI: 10.1136/ard.2005.043257]
40 **Tamori A**, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, Enomoto M, Inaba M, Nakatani T, Hino M, Kawada N. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. *J Gastroenterol* 2011; **46**: 556-564 [PMID: 21246383 DOI: 10.1007/s00535-010-0367-5]
41 **Urata Y**, Uesato R, Tanaka D, Kowatari K, Nitobe T, Nakamura Y, Motomura S. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. *Mod Rheumatol* 2011; **21**: 16-23 [PMID: 20668905 DOI: 10.1007/s10165-010-0337-z]
42 **Germanidis G**, Hytiroglou P, Zakalka M, Settas L. Reactivation of occult hepatitis B virus infection, following treatment of refractory rheumatoid arthritis with abatacept. *J Hepatol* 2012; **56**: 1420-1421 [PMID: 22127282 DOI: 10.1016/j.jhep.2011.10.011]
43 **Ryu HH**, Lee EY, Shin K, Choi IA, Lee YJ, Yoo B, Park MC, Park YB, Bae SC, Yoo WH, Kim SI, Lee EB, Song YW. Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNFα agents: a retrospective analysis of 49 cases. *Clin Rheumatol* 2012; **31**: 931-936 [PMID: 22349880 DOI: 10.1007/s10067-012-1960-1]
44 **Nakamura J**, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis* 2014; Epub ahead of print [PMID: 24698305 DOI: 10.1111/1756-185X.12359]
45 **Koskinas J**, Tampaki M, Doumba PP, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. *Br J Dermatol* 2013; **168**: 679-680 [PMID: 23121260 DOI: 10.1111/bjd.12120]
46 **Aubourg A**, d'Alteroche L, Senecal D, Gaudy C, Bacq Y. [Autoimmune thrombopenia associated with hepatitis B reactivation (reverse seroconversion) after autologous hematopoietic stem cell transplantation]. *Gastroenterol Clin Biol* 2007; **31**: 97-99 [PMID: 17273140 DOI: 10.1016/S0399-8320(07)89335-3]
47 **Kato M**, Atsumi T, Kurita T, Odani T, Fujieda Y, Otomo K, Horita T, Yasuda S, Koike T. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in Hepatitis B surface antigen-negative cases. *J Rheumatol* 2011; **38**: 2209-2214 [PMID: 21844146 DOI: 10.3899/jrheum.110289]
48 **Dusheiko G**, Song E, Bowyer S, Whitcutt M, Maier G, Meyers A, Kew MC. Natural history of hepatitis B virus infection in renal transplant recipients--a fifteen-year follow-up. *Hepatology* 1983; **3**: 330-336 [PMID: 6341196]
49 **Bain VG**. Hepatitis B in transplantation. *Transpl Infect Dis* 2000; **2**: 153-165 [PMID: 11429028]
50 **Gane E**, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. *Transplantation* 2002; **74**: 427-437 [PMID: 12352899 DOI: 10.1097/01.TP.0000020756.34168.E0]
51 **Kletzmayr J**, Watschinger B. Chronic hepatitis B virus infection in renal transplant recipients. *Semin Nephrol* 2002; **22**: 375-389 [PMID: 12118403]
52 **Berger A**, Preiser W, Kachel HG, Stürmer M, Doerr HW. HBV reactivation after kidney transplantation. *J Clin Virol* 2005; **32**: 162-165 [PMID: 15653420 DOI: 10.1016/j.jcv.2004.10.006]
53 **Yeo W**, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006; **43**: 209-220 [PMID: 16440366 DOI: 10.1002/hep.21051]
54 **Lalazar G**, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. *Br J Haematol* 2007; **136**: 699-712 [PMID: 17338776 DOI: 10.1111/j.1365-2141.2006.06465.x]
55 **Thomas HC**. Best practice in the treatment of chronic hepatitis B: a summary of the European Viral Hepatitis Educational Initiative (EVHEI). *J Hepatol* 2007; **47**: 588-597 [PMID: 17697725]
56 **Yeo W**, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, Lam KC, Johnson PJ. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004; **90**: 1306-1311 [PMID: 15054446 DOI: 10.1038/sj.bjc.6601699]
57 **Shouval D**, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis* 2013; **33**: 167-177 [PMID: 23749673 DOI: 10.1055/s-0033-1345722]
58 **Lok AS**, Lai CL. Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection. Incidence, predisposing factors and etiology. *J Hepatol* 1990; **10**: 29-34 [PMID: 2307827]
59 **Jazayeri MS**, Basuni AA, Cooksley G, Locarnini S, Carman WF. Hepatitis B virus genotypes, core gene variability and ethnicity in the Pacific region. *J Hepatol* 2004; **41**: 139-146 [PMID: 15246220 DOI: 10.1016/j.jhep.2004.03.025]
60 **Salpini R**, Colagrossi L, Bellocchi MC, Surdo M, Becker C, Alteri C, Aragri M, Ricciardi A, Armenia D, Pollicita M, Di Santo F, Carioti L, Louzoun Y, Mastroianni CM, Lichtner M, Paoloni M, Esposito M, D'Amore C, Marrone A, Marignani M, Sarrecchia C, Sarmati L, Andreoni M, Angelico M, Verheyen J, Perno CF, Svicher V. Hepatitis B surface antigen genetic elements critical for immune escape correlate with hepatitis B virus reactivation upon immunosuppression. *Hepatology* 2015; **61**: 823-833 [PMID: 25418031 DOI: 10.1002/hep.27604]
61 **Sanz I**. Indications of rituximab in autoimmune diseases. *Drug Discov Today Ther Strateg* 2009; **6**: 13-19 [PMID: 20379381 DOI: 10.1016/j.ddstr.2009.10.001]
62 **Dalakas MC**. B cells as therapeutic targets in autoimmune neurological disorders. *Nat Clin Pract Neurol* 2008; **4**: 557-567 [PMID: 18813230 DOI: 10.1038/ncpneuro0901]
63 **Perrillo RP**, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 221-244.e3 [PMID: 25447852 DOI: 10.1053/j.gastro.2014.10.038]
64 **Yeo W**, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, Chan HL, Hui EP, Lei KI, Mok TS, Chan PK. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; **27**: 605-611 [PMID: 19075267 DOI: 10.1200/JCO.2008.18.0182]
65 **Pei SN**, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, Kuo CY. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol* 2010; **89**: 255-262 [PMID: 19697028 DOI: 10.1007/s00277-009-0806-7]
66 **Nathan DM**, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. *J Gastroenterol Hepatol* 2006; **21**: 1366-1371 [PMID: 16911678 DOI: 10.1111/j.1440-1746.2006.04559.x]
67 **Pérez-Alvarez R**, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, Bové A, Bosch X, Sanchez-Tapias JM, Forns X, Ramos-Casals M. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine* (Baltimore) 2011; **90**: 359-371 [PMID: 22033451 DOI: 10.1097/MD.0b013e3182380a76]
68 **Lai GM**, Yan SL, Chang CS, Tsai CY. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase

inhibitor. *World J Gastroenterol* 2013; **19**: 1318-1321 [PMID: 23483799 DOI: 10.3748/wjg.v19.i8.1318]
69 **Ikeda K**, Shiga Y, Takahashi A, Kai T, Kimura H, Takeyama K, Noji H, Ogawa K, Nakamura A, Ohira H, Sato Y, Maruyama Y. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. *Leuk Lymphoma* 2006; **47**: 155-157 [PMID: 16321842 DOI: 10.1080/14639230500236818]
70 **Lakhani S**, Davidson L, Priebat DA, Sherker AH. Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. *Hepatol Int* 2008; **2**: 498-499 [PMID: 19669326 DOI: 10.1007/s12072-008-9099-5]
71 **Thia TJ**, Tan HH, Chuah TH, Chow WC, Lui HF. Imatinib mesylate-related fatal acute hepatic failure in a patient with chronic myeloid leukaemia and chronic hepatitis B infection. *Singapore Med J* 2008; **49**: e86-e89 [PMID: 18362995]
72 **Kang BW**, Lee SJ, Moon JH, Kim SN, Chae YS, Kim JG, Hwang YJ, Sohn SK. Chronic myeloid leukemia patient manifesting fatal hepatitis B virus reactivation during treatment with imatinib rescued by liver transplantation: case report and literature review. *Int J Hematol* 2009; **90**: 383-387 [PMID: 19641858 DOI: 10.1007/s12185-009-0386-2]
73 **Wang YD**, Cui GH, Li M, Gowrea B, Xia J, Hu Y. Hepatitis B virus reactivation in a chronic myeloid leukemia patient treated with imatinib mesylate. *Chin Med J* (Engl) 2012; **125**: 2636-2637 [PMID: 22882953]
74 **Walker EJ**, Simko JP, Ko AH. Hepatitis B viral reactivation secondary to imatinib treatment in a patient with gastrointestinal stromal tumor. *Anticancer Res* 2014; **34**: 3629-3634 [PMID: 24982379]
75 **Tur-Kaspa R**, Shaul Y, Moore DD, Burk RD, Okret S, Poellinger L, Shafritz DA. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. *Virology* 1988; **167**: 630-633 [PMID: 3201757 DOI: 10.1016/0042-6822(88)90127-4]
76 **Hoofnagle JH**, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, Waggoner JG, Jones EA, Seeff LB. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1986; **104**: 12-17 [PMID: 3940480 DOI: 10.7326/0003-4819-104-1-12]
77 **Kim TW**, Kim MN, Kwon JW, Kim KM, Kim SH, Kim W, Park HW, Chang YS, Cho SH, Min KU, Kim YY. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. *Respirology* 2010; **15**: 1092-1097 [PMID: 20630033 DOI: 10.1111/j.1440-1843.2010.01798.x]
78 **Flowers MA**, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, Levy GA, Inman RD. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; **112**: 381-382 [PMID: 2306066 DOI: 10.7326/0003-4819-112-5-381]
79 **Hagiyama H**, Kubota T, Komano Y, Kurosaki M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. *Clin Exp Rheumatol* 2004; **22**: 375-376 [PMID: 15144137]
80 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-219; quiz e16-17 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]
81 **Andersen ES**, Gerstoft J, Weis N. Reactivation of hepatitis D virus after chemotherapy for diffuse large B cell lymphoma despite lamivudine prophylaxis. *Int J Hematol* 2010; **92**: 378-380 [PMID: 20686876 DOI: 10.1007/s12185-010-0648-z]
82 **Lim LL**, Wai CT, Lee YM, Kong HL, Lim R, Koay E, Lim SG. Prophylactic lamivudine prevents hepatitis B reactivation in chemotherapy patients. *Aliment Pharmacol Ther* 2002; **16**: 1939-1944 [PMID: 12390103]
83 **Gwak GY**, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol* 2007; **25**: 888-889 [PMID: 18173926 DOI: 10.1007/s10067-013-2450-9]
84 **Simpson ND**, Simpson PW, Ahmed AM, Nguyen MH, Garcia G, Keeffe EB, Ahmed A. Prophylaxis against chemotherapy-induced reactivation of hepatitis B virus infection with Lamivudine. *J Clin Gastroenterol* 2003; **37**: 68-71 [PMID: 12811213]
85 **Law JK**, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida EM. Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. *Leuk Lymphoma* 2005; **46**: 1085-1089 [PMID: 16019563 DOI: 10.1080/10428190500062932]
86 **Inoue T**, Fuke H, Yamamoto N, Ito K, Yutaka KY, Yamanaka K. Lamivudine for treatment of spontaneous exacerbation and reactivation after immunosuppressive therapy in patients with hepatitis B virus infection. *Hepatogastroenterology* 2007; **54**: 889-891 [PMID: 17591085]
87 **Sanchez MJ**, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. *J Hepatol* 2009; **51**: 1091-1096 [PMID: 19836097 DOI: 10.1016/j.jhep.2009.07.012]
88 **Okagawa Y**, Takada K, Hisai H, Koshiba Y, Wada H, Miyazaki E, Kanari Y, Kawano Y, Iyama S, Hayashi T, Sato T, Sato Y, Miyanishi K, Kobune M, Takimoto R, Kato J. Successful treatment with entecavir for reactivation of hepatitis B virus following systemic chemotherapy in a hepatitis B surface antigen-negative patient with colorectal cancer. *Intern Med* 2014; **53**: 1759-1762 [PMID: 25130106 DOI: 10.2169/internalmedicine.53.1970]
89 **Türker K**, Albayrak M, Öksüzoğlu B, Balc E, Oğan MC, Iskender G, Altuntaş F. Entecavir as a first-line treatment for hepatitis B virus reactivation following polychemotherapy for chronic lymphocytic leukemia and invasive ductal carcinoma: a report of two cases and review of the literature. *Eur J Gastroenterol Hepatol* 2015; **27**: 39-45 [PMID: 25076063 DOI: 10.1097/meg.0000000000000115]
90 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948]
91 **Martyak LA**, Taqavi E, Saab S. Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis. *Liver Int* 2008; **28**: 28-38 [PMID: 17976155 DOI: 10.1111/j.1478-3231.2007.01618.x]
92 **Huang YH**, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, Yang MH, Tzeng CH, Lee PC, Lin HC, Lee SD. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013; **31**: 2765-2772 [PMID: 23775967 DOI: 10.1200/JCO.2012.48.5938]
93 **Jang JW**, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, Cho SH, Han JY, Lee YS. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemolipiodolization. *Hepatology* 2006; **43**: 233-240 [PMID: 16440357 DOI: 10.1002/hep.21024]
94 **Lau GK**, Yiu HH, Fong DY, Cheng HC, Au WY, Lai LS, Cheung M, Zhang HY, Lie A, Ngan R, Liang R. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology* 2003; **125**: 1742-1749 [PMID: 14724827]
95 **Long M**, Jia W, Li S, Jin L, Wu J, Rao N, Feng H, Chen K, Deng H, Liu F, Su F, Song E. A single-center, prospective and randomized controlled study: Can the prophylactic use of lamivudine prevent hepatitis B virus reactivation in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy? *Breast Cancer Res Treat* 2011; **127**: 705-712 [PMID: 21445574 DOI: 10.1007/s10549

-011-1455-9]
96 **Saab S**, Dong MH, Joseph TA, Tong MJ. Hepatitis B prophylaxis in patients undergoing chemotherapy for lymphoma: a decision analysis model. *Hepatology* 2007; **46**: 1049-1056 [PMID: 17680650 DOI: 10.1002/hep.21783]
97 **Endo T**, Sakai T, Fujimoto K, Yamamoto S, Takashima H, Haseyama Y, Nishio M, Koizumi K, Koike T, Sawada K. A possible role for lamivudine as prophylaxis against hepatitis B reactivation in carriers of hepatitis B who undergo chemotherapy and autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2001; **27**: 433-436 [PMID: 11313673 DOI: 10.1038/sj.bmt.1702804]
98 **Myers RP**, Swain MG, Urbanski SJ, Lee SS. Reactivation of hepatitis B e antigen-negative chronic hepatitis B in a bone marrow transplant recipient following lamivudine withdrawal. *Can J Gastroenterol* 2001; **15**: 599-603 [PMID: 11573103]
99 **Hsiao LT**, Chiou TJ, Liu JH, Chu CJ, Lin YC, Chao TC, Wang WS, Yen CC, Yang MH, Tzeng CH, Chen PM. Extended lamivudine therapy against hepatitis B virus infection in hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12**: 84-94 [PMID: 16399572 DOI: 10.1016/j.bbmt.2005.09.001]
100 **Moses SE**, Lim ZY, Sudhanva M, Devereux S, Ho AY, Pagliuca A, Zuckerman M, Mufti GJ. Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. *J Med Virol* 2006; **78**: 1560-1563 [PMID: 17063522 DOI: 10.1002/jmv.20705]
101 **Aoki J**, Kimura K, Kakihana K, Ohashi K, Sakamaki H. Efficacy and tolerability of Entecavir for hepatitis B virus infection after hematopoietic stem cell transplantation. *Springerplus* 2014; **3**: 450 [PMID: 25184113 DOI: 10.1186/2193-1801-3-450]
102 **Hashino S**, Nozawa A, Izumiyama K, Yonezumi M, Chiba K, Kondo T, Suzuki S, Hige S, Asaka M. Lamivudine treatment for reverse seroconversion of hepatitis B 4 years after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2002; **29**: 361-363 [PMID: 11896435 DOI: 10.1038/sj.bmt.1703387]
103 **European Association For The Study Of The Liver**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]
104 **Win LL**, Powis J, Shah H, Feld JJ, Wong DK. Death from Liver Failure despite Lamivudine Prophylaxis during R-CHOP Chemotherapy due to Rapid Emergence M204 Mutations. *Case Reports Hepatol* 2013; **2013**: 454897 [PMID: 25374716 DOI: 10.1155/2013/454897]
105 **Chen FW**, Coyle L, Jones BE, Pattullo V. Entecavir versus lamivudine for hepatitis B prophylaxis in patients with haematological disease. *Liver Int* 2013; **33**: 1203-1210 [PMID: 23522150 DOI: 10.1111/liv.12154]
106 **Kojima H**, Tsujimura H, Sugawara T, Mimura N, Ise M, Sakai C, Yamada S, Miyaki T, Kumagai K. 521 Prospective Study of Hepatitis B Virus Reactivation in Hbsag-Negative Patients after Chemotherapy with Rituximab: HBV-DNA Monitoring and Entecavir Prophylaxis. *J Hepatol* 2012; **56**: S206 [DOI: 10.1016/s0168-8278(12)60534-0]
107 **Li HR**, Huang JJ, Guo HQ, Zhang X, Xie Y, Zhu HL, Zhai LZ, Pu XX, Huang Y, Guo CC, Lin TY. Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy. *J Viral Hepat* 2011; **18**: 877-883 [PMID: 21054683 DOI: 10.1111/j.1365-2893.2010.01386.x]
108 **Kim SJ**, Hsu C, Song YQ, Tay K, Hong XN, Cao J, Kim JS, Eom HS, Lee JH, Zhu J, Chang KM, Reksodiputro AH, Tan D, Goh YT, Lee J, Intragumtornchai T, Chng WJ, Cheng AL, Lim ST, Suh C, Kwong YL, Kim WS. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer* 2013; **49**: 3486-3496 [PMID: 23910494 DOI: 10.1016/j.ejca.2013.07.006]
109 **Liaw YF**, Kao JH, Piratvisuth T, Chan HLY, Chien RN, Liu CJ, Gane E, Locarnini S, Lim SG, Han KH, Amarapurkar D, Cooksley G, Jafri W, Mohamed R, Hou JL, Chuang WL, Lesmana LA, Sollano JD, Suh D-J, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepa Inter* 2012; **6**: 531-561 [DOI: 10.1007/s12072-012-9365-4]
110 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
111 **Artz AS**, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, Zon RT, Wong SL. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol* 2010; **28**: 3199-3202 [PMID: 20516452 DOI: 10.1200/JCO.2010.30.0673]

P- Reviewer: Stalke P, Wang K **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com