

# Management of hepatitis B reactivation in patients receiving cancer chemotherapy

Yi-Wen Huang and Raymond T. Chung

**Abstract:** Hepatitis B virus (HBV) reactivation is well documented in previously resolved or inactive HBV carriers who receive cancer chemotherapy. The consequences of HBV reactivation range from self-limited conditions to fulminant hepatic failure and death. HBV reactivation also leads to premature termination of chemotherapy or delay in treatment schedules. This review summarizes current knowledge of management of HBV reactivation in patients receiving cancer chemotherapy. HBV surface antigen (HBsAg) testing should be performed in patients who require cancer chemotherapy. Four meta-analyses support lamivudine prophylaxis for HBV reactivation during chemotherapy in HBsAg-positive patients. Randomized controlled trials to compare different HBV antiviral agents are needed to define optimal regimens for the prevention and treatment of HBV reactivation in patients receiving cancer chemotherapy.

**Keywords:** cancer, chemotherapy, HBV reactivation, hepatitis B virus, lamivudine, prophylaxis

## Introduction

There are 400 million chronic carriers of hepatitis B virus (HBV) worldwide and 800,000 to 1.4 million in the US [Sorrell *et al.* 2009; Weinbaum *et al.* 2009]. Approximately half to two thirds of HBV carriers in US were born in other countries [Weinbaum *et al.* 2009]. HBV reactivation has been well documented in previously resolved or inactive HBV carriers who receive cancer chemotherapy. The consequences of HBV reactivation range from a self-limited hepatitis to fulminant hepatic failure and death [Liang *et al.* 1990; Galbraith *et al.* 1975; Pinto *et al.* 1990; Yeo *et al.* 2009]. HBV reactivation also necessitates premature termination of chemotherapy or delay in treatment schedules [Yeo *et al.* 2003, 2005]. Several factors have served to further accentuate the clinical importance of HBV reactivation: (1) advances in potent chemotherapy for cancer; (2) the increasing utilization of immunosuppressive agents in transplantation or autoimmune diseases; (3) the increasing influx of immigrants from HBV high endemic to low endemic areas; and (4) a potentially fatal outcome that is readily preventable with prophylactic antiviral treatment. This work reviews current concepts regarding management of HBV reactivation in patients receiving cancer chemotherapy. A PubMed search

with the keywords 'hepatitis B' AND 'chemotherapy' was conducted to retrieve published articles focused on natural history, pathogenesis, prevention and treatment of HBV reactivation.

## Natural history of HBV reactivation

### Definition of HBV reactivation

HBV reactivation is defined as an abrupt increase in serum HBV DNA and alanine transaminase (ALT) levels in a patient with resolved or inactive HBV infection [Hoofnagle, 2009; Lok and McMahon, 2009]. In patients with negative HBV surface antigen (HBsAg) and positive antibody to HBV core antigen (anti-HBc), HBV reactivation, termed *de novo* hepatitis, is defined as HBsAg reappearance with threefold elevated ALT on two consecutive tests 5 days apart and accompanied by an increase in HBV DNA to more than  $10^5$  copies/ml [Hui *et al.* 2006].

### Epidemiology

The incidence of HBV reactivation in HBsAg positive patients receiving cancer chemotherapy has been reported to range from 20% to 57% [Kim *et al.* 2007; Kumagai *et al.* 1997; Yeo *et al.* 2000a,

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2000b, 2003]. HBV reactivation was observed in 50% of HBsAg-positive patients receiving rituximab-based therapy [Mendez-Navarro *et al.* 2011]. Reactivation does not necessarily require receipt of systemic chemotherapy. For instance, the reactivation rate in those receiving transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) has been reported to be as high as 34% [Jang *et al.* 2004].

Reactivation can be seen in persons with past exposure who do not harbor active HBV. The HBV reactivation rate in subjects with negative HBsAg and positive anti-HBc was 3% [Hui *et al.* 2006], and ranges from 2% to 25% in those receiving rituximab-based therapy [Ji *et al.* 2010; Koo *et al.* 2011; Matsue *et al.* 2010; Yeo *et al.* 2009].

#### *Clinical features of HBV reactivation*

In hematologic malignancies, early reports with serial follow up of HBV serologic markers observed reduction of antibody titers to HBV with subsequent reappearance of HBV antigen in 29% of patients under cancer chemotherapy. In addition, HBsAg was persistent in 40% of them and an increase in antigen titer was associated with elevated ALT [Wands *et al.* 1975]. Elevation in HBsAg titer was noted in 83% of patients with hematologic malignancies who received glucocorticoids [Ohtsu *et al.* 1991]. During follow up for up to 1 year after cancer chemotherapy, loss of antibody to HBV surface antigen (anti-HBs) was observed in 1% [Alexopoulos *et al.* 1999].

In breast cancer patients receiving doxorubicin and cyclophosphamide who were premedicated with dexamethasone, serum HBV DNA peaked prior to ALT by nearly 2 weeks [Yeo *et al.* 2001]. In contrast, serum HBV DNA rose 5–8 weeks prior to the ALT in chronic HBV patients with spontaneous reactivation [Maruyama *et al.* 1993] and in those treated with corticosteroid alone, 4 weeks in advance of peak ALT [Nair *et al.* 1986].

In *de novo* HBV-related hepatitis, a hundredfold rise in serum HBV DNA preceded threefold elevated ALT by 12 to 28 weeks [Hui *et al.* 2006]. HBsAg seroreversion developed after rise in serum HBV DNA and before ALT elevation [Hui *et al.* 2006]. Rituximab plus steroid is an independent factor associated with *de novo* HBV-related hepatitis [Hui *et al.* 2006]. Thus, patients with negative HBsAg and positive anti-HBc need a much longer interval to develop clinical hepatitis

as compared with those with positive HBsAg. This late onset of clinical hepatitis suggests a delayed immune recovery because of the prolonged suppressive effects of rituximab [Dai *et al.* 2004a]. Rituximab-induced deficiency in antigen-presenting cells which led the HBV to escape the control of cytotoxic T-lymphocyte [Hui *et al.* 2006].

Serial serum HBV DNA and ALT monitoring before and during chemotherapy is important for a timely diagnosis of HBV reactivation. Since HBV DNA elevation precedes ALT elevation in both HBsAg-positive and HBsAg-negative/anti-HBc-positive patients (Figure 1), vigilance for HBV DNA during chemotherapy is essential so that prompt preemptive antiviral therapy may be instituted.

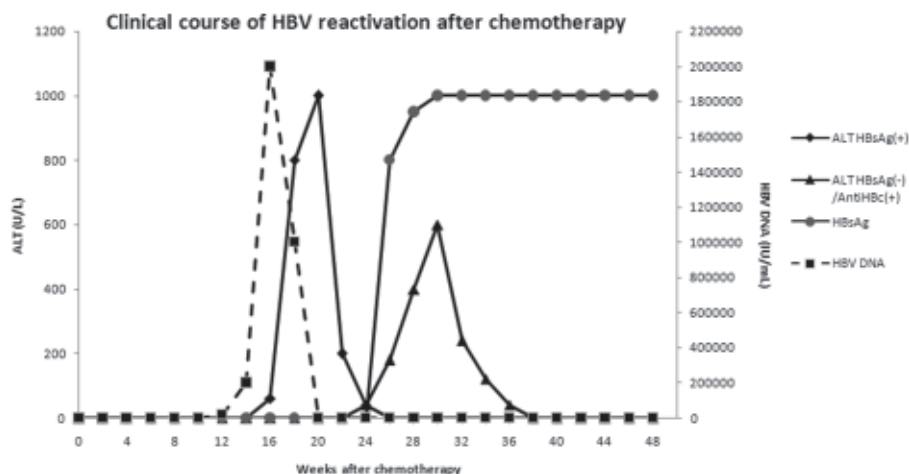
#### *Risk factors for HBV reactivation*

HBV reactivation has been observed in patients receiving chemotherapy for hematologic malignancy [Galbraith *et al.* 1975; Yeo *et al.* 2009; Hwang *et al.* 2011], breast cancer [Kim *et al.* 2007; Yeo *et al.* 2003], hepatocellular carcinoma (HCC) [Nagamatsu *et al.* 2003; Yeo *et al.* 2004c], nasopharyngeal carcinoma [Yeo *et al.* 2005], and chemoradiation in postgastrectomy for gastric/esophageal adenocarcinoma [Cheng *et al.* 2004].

The risks of HBV reactivation in patients with positive HBsAg and negative HBsAg/positive anti-HBc are shown in Table 1. The cutoff level of serum HBV DNA between HBsAg-positive patients with *versus* without reactivation was  $3 \times 10^5$  copies/ml [Zhong *et al.* 2004]. One of the modifiable risks among the risk factors for HBsAg-positive patients may be glucocorticoid use. This may be due to steroid increased HBV replication through glucocorticoid responsive element in HBV genome which enhances HBV replication greatly. In this regard, steroid-free regimens in HBsAg-positive patients with lymphoma were associated with reduced incidence and severity of HBV reactivation [Cheng *et al.* 2003].

#### *Consequences of HBV reactivation*

HBV reactivation has been associated with jaundice in 10% of patients [Liang *et al.* 1990], fulminant hepatic failure in 6% [Liang *et al.* 1990] and death [Galbraith *et al.* 1975; Pinto *et al.* 1990; Yeo *et al.* 2009]. In fulminant hepatic failure or severe



**Figure 1.** Typical clinical course of HBV reactivation in HBsAg-positive and HBsAg-negative/anti-HBc-positive individuals receiving chemotherapy. In HBsAg-positive patients, serum HBV DNA was undetectable at the time of peak ALT, instead, it peaked prior to ALT by around 2 weeks [Yeo *et al.* 2001]. In HBsAg-negative/anti-HBc-positive subjects, serum HBV DNA preceded elevated ALT by 12–28 weeks [Hui *et al.* 2006]. HBsAg seroreversion developed after rise in serum HBV DNA and before ALT elevation [Hui *et al.* 2006]. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; ALT, alanine transaminase.

**Table 1.** Risks for HBV reactivation in patients with positive HBsAg and negative HBsAg/positive anti-HBc.

Risks for HBV reactivation in patients with positive HBsAg	[References]
<i>Patient specific</i>	
Male gender	[Yeo <i>et al.</i> 2000a]
Younger age	[Yeo <i>et al.</i> 2000a]
Elevated baseline ALT	[Yeo <i>et al.</i> 2004c]
<i>Viral related</i>	
Positive HBeAg	[Yeo <i>et al.</i> 2000a]
Precore mutation	[Yeo <i>et al.</i> 2000b]
Prechemotherapy HBV DNA	[Yeo <i>et al.</i> 2004d; Zhong <i>et al.</i> 2004]
<i>Treatment related</i>	
Glucocorticoid use	[Cheng <i>et al.</i> 2003; Nakamura <i>et al.</i> 1996; Ohtsu <i>et al.</i> 1991; Yeo <i>et al.</i> 2004d]
Anthracyclines use	[Yeo <i>et al.</i> 2004d]
TACE treatment for HCC	[Jang <i>et al.</i> 2004]
<i>Cancer type</i>	
Lymphoma	[Yeo <i>et al.</i> 2000a; Yeo <i>et al.</i> 2004d]
Breast cancer	[Yeo <i>et al.</i> 2004d]
<i>Risks for HBV reactivation in patients with negative HBsAg / positive anti-HBc</i>	
Male gender	[Yeo <i>et al.</i> 2009]
Rituximab use and negative anti-HBs	[Matsue <i>et al.</i> 2010; Yeo <i>et al.</i> 2009]

(Continued)

**Table 1.** (Continued)

Multivariate analysis of risks for HBV reactivation in patients with positive HBsAg		
Variable	OR (95% CI)	[Yeo <i>et al.</i> 2004d]
Prechemotherapy detectable HBV DNA	8.4 (2.6–27.2)	
Lymphoma	5.0 (1.1–23.5)	
Breast cancer	4.2 (1.6–11.0)	
Glucocorticoid use	2.7 (1.0–7.2)	
Multivariate analysis of risks for HBV reactivation in patients with negative HBsAg		
Variable	ARR (95% CI)	[Hui <i>et al.</i> 2006]
Rituximab plus steroid-containing regimen:		<i>p</i> -value
Yes	13.8 (2.8–68.3)	0.001
No	1	
Steroid-containing regimen:		0.105
Yes	5.0 (0.6–40.9)	
No	1	
Rituximab-containing regimen:		0.263
Yes	1.3 (0.1–20.4)	
No	1	
Anti-HBc status prechemotherapy:		0.190
Positive	3.7 (0.5–30.2)	
Negative	1	

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B extracellular antigen; ALT, alanine transaminase; TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; OR, odds ratio; ARR, adjusted relative risk; CI, confidence interval.

hepatitis, patients harboring precore mutations had increased risk compared with those without these mutants [Dai *et al.* 2001; Steinberg *et al.* 2000]. The overall liver related mortality associated with reactivation has been estimated to be 5% [Liang *et al.* 1990], with high mortality rates (30%) in patients with HCC [Yeo *et al.* 2004c]. Around 11% of HCC patients receiving TACE died of hepatic decompensation due to HBV reactivation [Jang *et al.* 2004]. In patients with *de novo* HBV-related hepatitis, fulminant hepatic failure developed in 38% [Hui *et al.* 2006]. In addition, patients with HBV reactivation had delays or interruption of chemotherapy schedule or premature termination in 68–71% versus 19–33% of those without [Yeo *et al.* 2003, 2005], which may itself be associated with decreased cancer survival.

#### Pathogenesis of HBV reactivation

The underlying mechanism of HBV reactivation during cancer chemotherapy remains unclear. The reactivation is consistent with replication

induced from latent forms of HBV even after serologic evidence of viral clearance [Hoofnagle, 2009]. It has been generally hypothesized that cancer chemotherapy leads to widespread HBV infection in hepatocytes by enhancing replication and suppressing the cellular immune response to the virus. Subsequent resurgence of immune function following chemotherapy discontinuation then results in rapid destruction of all infected hepatocytes [Galbraith *et al.* 1975; Xunrong *et al.* 2001].

In support of this premise are data demonstrating that direct exposure of HBV-expressing human hepatoma 1.3ES2 cells to doxorubicin or etoposide increased HBV DNA replication and HBV pregenomic transcription [Chung and Tsai, 2009]. Furthermore, HBV replication during chemotherapy is associated with activation of DNA repair pathways. Activation of chemotherapy-induced DNA repair signaling upregulated promyelocytic leukemia protein in its nuclear body (PML-NB) and the upregulated PML-NB initiated HBV replication [Chung and Tsai, 2009].

## Prevention and treatment

### Screening

The National Institutes of Health Consensus Development Conference Statement recommends routine screening for hepatitis B of newly arrived immigrants to the US from countries where the HBV prevalence rate is intermediate or high (i.e. greater than 2%) [Sorrell *et al.* 2009]. The US Centers for Disease Control and Prevention (CDC) also recommend testing of persons born in geographic regions with HBsAg prevalence of greater than 2% [Weinbaum *et al.* 2009]. The CDC recommends testing for HBsAg, anti-HBc and anti-HBs for all patients before the receipt of chemotherapy [Weinbaum *et al.* 2009]. The American Society of Clinical Oncology provisional clinical opinion suggested testing for HBsAg on high risk of previous HBV exposure or reactivation and testing for anti-HBc in some but not all patients [Artz *et al.* 2010]. However, testing for anti-HBs was not supported by evidence [Artz *et al.* 2010]. In patients with solid tumors who require chemotherapy, testing for HBsAg alone was the most economical strategy [Day *et al.* 2011]. For patients with reported HBV reactivation rates of more than or equal to 41% as in HBsAg-positive patients receiving rituximab-based therapy and in populations with expected HBsAg prevalence of 2.7%, testing for HBsAg and anti-HBc maximized cost-effectiveness [Day *et al.* 2011].

In clinical practice, a retrospective study in US showed that only 17% of cancer patients were screened for HBsAg and anti-HBc prior to chemotherapy [Hwang *et al.* 2011]. Testing for HBV has not been adequately performed in patients at risk for HBV in US.

### Prevention and treatment

Lamivudine is a nucleoside analogue that effectively suppresses HBV replication. Four meta-analyses have supported lamivudine prophylaxis for HBV reactivation during chemotherapy in HBsAg-positive patients (Table 2). All studies included in these four meta-analyses showed a lower rate of HBV reactivation in patients receiving lamivudine prophylaxis (Table 2). The earliest analysis revealed prophylactic lamivudine decreased HBV reactivation by fourfold to sevenfold [Kohrt *et al.* 2006]. Two other meta-analyses, with much overlap in the studies included in both analyses, showed that lamivudine reduced

the risk for HBV reactivation by 80–87% and reactivation-related mortality by 70% over no or deferred lamivudine use [Loomba *et al.* 2008; Martyak *et al.* 2008]. Preventive lamivudine also reduced treatment delays and premature termination of chemotherapy by 59% [Martyak *et al.* 2008]. A recent meta-analysis focused on lymphoma confirmed the efficacy of prophylactic lamivudine in reducing HBV reactivation [Ziakas *et al.* 2009]. Prophylactic lamivudine also reduced the severity of chemotherapy-related HBV reactivation in patients with solid tumors as well as lymphoma in a randomized trial and a retrospective study [Hsu *et al.* 2008; Yun *et al.* 2011]. A more recent retrospective study did not support the use of prophylactic lamivudine in HBsAg-negative anti-HBc-positive individuals receiving chemotherapy or rituximab [Koo *et al.* 2010] given the low frequency of this event [Hui *et al.* 2006].

### Timing and duration of therapy

The optimal duration of preventive lamivudine remains unclear. Discontinuation of preventive lamivudine at 3 months after completion of chemotherapy resulted in a 24% rate of HBV reactivation [Hui *et al.* 2005]. Prechemotherapy serum HBV DNA of  $\geq 10^4$  copies/ml predicted reactivation after discontinuation [Hui *et al.* 2005]. In a decision analysis, extended lamivudine prophylaxis for 2 years throughout rituximab maintenance therapy improved 3-year overall survival rates by 2.4% in HBsAg-positive patients [Ziakas *et al.* 2009]. A cost-effectiveness study supported prophylactic lamivudine in HBsAg-positive patients with lymphoma 1 week before chemotherapy and for 6 months after the discontinuation of chemotherapy [Saab *et al.* 2007].

The use of lamivudine is limited by the development of resistance mutations that may contribute to hepatic decompensation and liver failure. The frequency of lamivudine resistance ranges from 3% to 8% in HBsAg-positive patients with hematologic malignancies under prophylactic use [Hsu *et al.* 2008; Pelizzari *et al.* 2004]. Adefovir has lower primary resistance rates and has been shown to be effective against lamivudine-resistant HBV strains. Two case reports of successful adefovir use either alone or in combination with lamivudine in patients with HBV reactivation under cancer chemotherapy have been reported [Cortezzi *et al.* 2006; Perez-Roldan *et al.* 2005]. Entecavir is a more potent inhibitor of HBV replication with a very low long-term rate of

**Table 2.** Meta-analyses on lamivudine prophylaxis for HBV reactivation during chemotherapy in HBsAg-positive patients.

Meta-analyses		Studies included											
Study design	RCT	Lmv E/N	No E/N	RR [95%CI]	Prospective	Lmv E/N	No E/N	RR [95%CI]	Retrospective	Lmv E/N	No E/N	RR [95%CI]	
Kohrt et al. [2006]	Lau et al. [2003]	0/15	8/15		Idilman et al. [2004]	0/8	5/10						
		1/6	0		Dai et al. [2004b]	1/6	0						
		0/11	5/9		Dai et al. [2004c]	0/11	5/9						
		2/31	19/61		Yeo et al. [2004b]	2/31	19/61						
		0/16	6/21		Yeo et al. [2005]	0/16	6/21						
		0/10	0		el-Sayed et al. [2004]	0/10	0						
		11/46	0		Hui et al. [2005]	11/46	0						
		1/20	0		Rossi et al. [2001]	1/20	0						
		0/10	0		Vassiliadis et al. [2005]	0/10	0						
		1/8	7/8	0.14 [0.01-0.67]	Jia and Lin [2004]	1/8	7/8	0.14 [0.01-0.67]	Lim et al. [2002]	0/16	7/19	0.00 [0.00-0.56]	
Loomba et al. [2008]	Lau et al. [2003]	0/15	8/15	0.00 [0.00-0.39]									
		1/36	15/37	0.07 [0.01-0.35]	Idilman et al. [2004]	0/8	5/10	0.00 [0.00-0.79]	Leaw et al. [2004]	0/11	17/53	0.00 [0.00-0.86]	
		3/26	14/25	0.21 [0.04-0.59]	Shibolet et al. [2002]	0/9	2/5	0.00 [0.00-1.31]	Nagamatsu et al. [2004]	0/8	6/9	0.00 [0.00-0.66]	
					Dai et al. [2004c]	0/11	5/9	0.00 [0.00-0.61]	Lee et al. [2003]	1/11	17/20	0.11 [0.01-0.46]	
					Yeo et al. [2004a]	3/65	47/193	0.19 [0.04-0.52]					
					Yeo et al. [2005]	0/16	6/21	0.00 [0.00-0.75]					



Table 2. (Continued)

Study design	Meta-analyses				Studies included							
	RCT	Lmv E/N	No E/N	RR [95%CI]	Prospective	Lmv E/N	No E/N	RR [95%CI]	Retrospective	Lmv E/N	No E/N	RR [95%CI]
Martyak <i>et al.</i> [2008]	Lau <i>et al.</i> [2003]	0/15	8/15		Idilman <i>et al.</i> [2004]	0/8	5/10		Lim <i>et al.</i> [2002]	0/16	7/19	
	Jang <i>et al.</i> [2006]	1/36	15/37		Dai <i>et al.</i> [2004c] Yeo <i>et al.</i> [2004b] Yeo <i>et al.</i> [2004a] Yeo <i>et al.</i> [2005]	0/11 2/31 3/65 0/16	5/9 19/61 47/193 6/21		Lee <i>et al.</i> [2003] Sugimoto <i>et al.</i> [2004]	1/11 0/5	17/20 6/6	
Ziakas <i>et al.</i> [2009]*	Lau <i>et al.</i> [2003]	0/15	8/15	0.06 [0.00–0.94]	Idilman <i>et al.</i> [2004]	0/4	2/3	0.16 [0.01–2.47]	Leaw <i>et al.</i> [2004]	0/11	17/53	0.13 [0.01–1.99]
	Hsu <i>et al.</i> [2008]	3/26	14/25	0.21 [0.07–0.63]	Shibolet <i>et al.</i> [2002]	0/7	2/4	0.13 [0.01–2.10]	Lee <i>et al.</i> [2003] Li <i>et al.</i> [2006]	1/11 7/40	17/20 60/116	0.11 [0.02–0.70] 0.34 [0.17–0.68]
									Persico <i>et al.</i> [2002] Tsutsumi <i>et al.</i> [2009]	0/3 0/10	12/18 4/15	0.19 [0.01–2.59] 0.16 [0.01–2.71]

RCT, randomized controlled trial; Lmv, lamivudine prophylaxis; No, no prophylaxis; E/N, events/total number; RR, relative risk; HBsAg, hepatitis B surface antigen.  
\*Lymphoma patients.

**Table 3.** Recommendations for management of HBV reactivation in patients receiving cancer chemotherapy.

1. HBsAg testing should be performed in patients who require cancer chemotherapy or a finite course of immunosuppressive agents.
2. Patients who require rituximab therapy or transplantation should be tested for HBsAg and anti-HBc.
3. Serum HBV DNA and ALT should be monitored every 1–3 months during and at least 6 months after completion of chemotherapy or immunosuppressive agents. Since HBV DNA precedes ALT, vigilance for HBV DNA is essential.
4. Prophylactic antiviral medication should be given to HBsAg positive patients before cancer chemotherapy or immunosuppressive agents.
5. Antiviral medication should be continued for 6 months after completion of cancer chemotherapy or immunosuppressive agents.
6. Chronic HBV patients with prechemotherapy serum HBV DNA of  $\geq 2000$  IU/ml should continue antiviral medication until:
  - a. HBeAg-positive patients: 6 months after HBeAg loss and anti-HBe detection.
  - b. HBeAg-negative patients: HBsAg clearance.
7. Antiviral medication should be given to HBsAg negative patients as soon as abrupt serum HBV DNA elevation is detected during cancer chemotherapy or immunosuppressive agents. Antiviral medication may be given to HBsAg-negative, anti-HBc-positive, anti-HBs-negative patients who receive rituximab.
8. The choice of antiviral medication can be based on the anticipated duration of treatment: lamivudine or telbivudine for duration of  $\leq 12$  months with undetectable serum HBV DNA and entecavir or tenofovir for longer duration or for patients with detectable HBV DNA prior to chemotherapy.

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B extracellular antigen; ALT, alanine transaminase.

primary resistance [Chang *et al.* 2006]. A retrospective multicenter study indicated that entecavir was superior to lamivudine in preventing HBV reactivation in lymphoma patients [Li *et al.* 2011]. Based on the anticipated duration of treatment, AASLD Practice Guidelines currently recommend lamivudine or telbivudine for a planned duration of  $\leq 12$  months, while tenofovir or entecavir are recommended for longer planned duration [Lok and McMahon, 2009]. Randomized controlled trials to compare different HBV antiviral agents are needed to establish optimal drug regimens for prevention and treatment of HBV reactivation in patients receiving cancer chemotherapy. Case reports described liver transplantation as a life-saving option for patients with liver failure due to HBV reactivation when the prognosis of the coexistent malignancy is good [Kim *et al.* 2010; King and Chung, 2010; Noterdaeme *et al.* 2011].

### Discussion

The time to discontinue prophylactic lamivudine has been suggested as 6 months after completion of chemotherapy in a cost-effectiveness study [Saab *et al.* 2007]. A shorter duration of 3 months resulted in high HBV reactivation rate in a longitudinal follow-up study [Hui *et al.* 2005], whereas

an extended duration for 2 years improved 3-year overall survival rates in a decision analysis by only 2.4% [Ziakas *et al.* 2009]. Therefore, prophylactic lamivudine should be continued for 6 months after completion of chemotherapy (Table 3), however, in patients with prechemotherapy serum HBV DNA of  $\geq 2000$  IU/ml, extended lamivudine use is recommended (Table 3). Further study is needed to determine the timing of treatment cessation in: (1) prophylactic use of antiviral agents with higher potency; and (2) HBsAg-negative patients receiving antiviral agents for serum HBV DNA elevation during chemotherapy. Data on monitoring following treatment discontinuation as well as management of reactivation in hepatitis B and delta co-infection have also been limited.

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### Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.



## References

- Alexopoulos, C.G., Vaslamatzis, M. and Hatzidimitriou, G. (1999) Prevalence of hepatitis B virus marker positivity and evolution of hepatitis B virus profile, during chemotherapy, in patients with solid tumours. *Br J Cancer* 81: 69–74.
- Artz, A.S., Somerfield, M.R., Feld, J.J., Giusti, A.F., Kramer, B.S., Sabichi, A.L., *et al.* (2010) 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* 28: 3199–3202.
- Chang, T.T., Gish, R.G., de Man, R., Gadano, A., Sollano, J., Chao, Y.C., *et al.* (2006) A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 354: 1001–1010.
- Cheng, J.C., Liu, M.C., Tsai, S.Y., Fang, W.T., Jer-Min Jian, J. and Sung, J.L. (2004) Unexpectedly frequent hepatitis B reactivation by chemoradiation in postgastrectomy patients. *Cancer* 101: 2126–2133.
- Cheng, A.L., Hsiung, C.A., Su, I.J., Chen, P.J., Chang, M.C., Tsao, C.J., *et al.* (2003) Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 37: 1320–1328.
- Chung, Y.L. and Tsai, T.Y. (2009) Promyelocytic leukemia nuclear bodies link the DNA damage repair pathway with hepatitis B virus replication: implications for hepatitis B virus exacerbation during chemotherapy and radiotherapy. *Mol Cancer Res* 7: 1672–1685.
- Cortelezzi, A., Vigano, M., Zilioli, V.R., Fantini, N.N., Pasquini, M.C., Deliliers, G.L., *et al.* (2006) Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H. *J Clin Virol* 35: 467–469.
- Dai, M.S., Lu, J.J., Chen, Y.C., Perng, C.L. and Chao, T.Y. (2001) Reactivation of precore mutant hepatitis B virus in chemotherapy-treated patients. *Cancer* 92: 2927–2932.
- Dai, M.S., Chao, T.Y., Kao, W.Y., Shyu, R.Y. and Liu, T.M. (2004a) Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. *Ann Hematol* 83:769–774.
- Dai, M.S., Wu, P.F., Lu, J.J., Shyu, R.Y. and Chao, T.Y. (2004b) Preemptive use of lamivudine in breast cancer patients carrying hepatitis B virus undergoing cytotoxic chemotherapy: a longitudinal study. *Support Care Cancer* 12: 191–196.
- Dai, M.S., Wu, P.F., Shyu, R.Y., Lu, J.J. and Chao, T.Y. (2004c) Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. *Liver Int* 24: 540–546.
- Day, F.L., Karnon, J. and Rischin, D. (2011) Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin Oncol* 29: 3270–3277.
- el-Sayed, M.H., Shanab, G., Karim, A.M., el-Tawil, A., Black, A. and Dixon, J.S. (2004) Lamivudine facilitates optimal chemotherapy in hepatitis B virus-infected children with hematological malignancies: a preliminary report. *Pediatr Hematol Oncol* 21: 145–156.
- Galbraith, R.M., Eddleston, A.L., Williams, R. and Zuckerman, A.J. (1975) Fulminant hepatic failure in leukemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. *Lancet* 2: 528–530.
- Hoofnagle, J.H. (2009) Reactivation of hepatitis B. *Hepatology* 49: S156–S165.
- Hsu, C., Hsiung, C.A., Su, I.J., Hwang, W.S., Wang, M.C., Lin, S.F., *et al.* (2008) A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 47: 844–853.
- Hsu, C., Sur, I.J., Hwang, W.S., Wang, M.C., Lin, S.F., Lin, T.H., *et al.* (2006) A prospective comparative study of prophylactic or therapeutic use of lamivudine for chemotherapy-associated hepatitis B (HBV) reactivation in non-Hodgkin's lymphoma patients [Abstract]. *Gastroenterology* 131: S297.
- Hui, C.K., Cheung, W.W., Au, W.Y., Lie, A.K., Zhang, H.Y., Yueng, Y.H., *et al.* (2005) Hepatitis B reactivation after withdrawal of pre-emptive lamivudine in patients with haematological malignancy on completion of cytotoxic chemotherapy. *Gut* 54: 1597–1603.
- Hui, C.K., Cheung, W.W., Zhang, H.Y., Au, W.Y., Yueng, Y.H., Leung, A.Y., *et al.* (2006) Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology* 131: 59–68.
- Hwang, J.P., Fisch, M.J., Zhang, H., Kallen, M.A., Routbort, M., Lal, L.S., *et al.* (2011) Reactivation of hepatitis B infection among patients with cancer [Abstract]. *Hepatology* 54: 445A.
- Idilman, R., Arat, M., Soydan, E., Toruner, M., Soykan, I., Akbulut, H., *et al.* (2004) Lamivudine prophylaxis for prevention of chemotherapy-induced hepatitis B virus reactivation in hepatitis B virus carriers with malignancies. *J Viral Hepat* 11: 141–147.
- Jang, J.W., Choi, J.Y., Bae, S.H., Kim, C.W., Yoon, S.K., Cho, S.H., *et al.* (2004) Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. *J Hepatol* 41: 427–435.

- Jang, J.W., Choi, J.Y., Bae, S.H., Yoon, S.K., Chang, U.I., Kim, C.W., *et al.* (2006) A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology* 43: 233–240.
- Ji, D., Cao, J., Hong, X., Li, J., Wang, J., Chen, F., *et al.* (2010) Low incidence of hepatitis B virus reactivation during chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative / HBeAb-positive: a multicenter retrospective study. *Eur J Haematol* 85: 243–250.
- Jia, J. and Lin, F. (2004) Lamivudine therapy for prevention of chemotherapy-induced reactivation of hepatitis B virus. *Zhonghua Gan Zang Bing Za Zhi* 12: 628–629.
- Kim, M.K., Ahn, J.H., Kim, S.B., Im, Y.S., Lee, S.I., Ahn, S.H., *et al.* (2007) Hepatitis B reactivation during adjuvant anthracycline-based chemotherapy in patients with breast cancer: a single institution's experience. *Korean J Intern Med* 22: 237–243.
- Kim, S.G., Chun, J.M., Jin, R., Kim, J.Y., Won, D.I. and Hwang, Y.J. (2010) Living donor liver transplantation for acute hepatic failure caused by reactivation of hepatitis B virus infection after chemotherapy for hematologic malignancy: case reports. *Transplant Proc* 42: 843–845.
- King, L.Y. and Chung, R.T. (2010) When treating cancer, please don't forget hepatitis B. *Oncologist* 15: 826–829.
- Kohrt, H.E., Ouyang, D.L. and Keeffe, E.B. (2006) Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 24: 1003–1016.
- Koo, Y.X., Tan, D.S., Tan, I.B., Tao, M., Chow, W.C. and Lim, S.T. (2010) Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. *Cancer* 116: 115–121.
- Koo, Y.X., Tay, M., The, Y.E., Teng, D., Tan, D.S., Tan, I.B., *et al.* (2011) Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. *Ann Hematol* 90: 1219–1223.
- Kumagai, K., Takagi, T., Nakamura, S., Sawada, U., Kura, U., Kodama, F., *et al.* (1997) Hepatitis B virus carriers in the treatment of malignant lymphoma: an epidemiological study in Japan. *Ann Oncol* 8(Suppl. 1): 107–109.
- Lau, G.K., Yiu, H.H., Fong, D.Y., Cheng, H.C., Au, W.Y., Lai, L.S., *et al.* (2003) Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology* 125: 1742–1749.
- Leaw, S.J., Yen, C.J., Huang, W.T., Chen, T.Y., Su, W.C. and Tsao, C.J. (2004) Preemptive use of interferon or lamivudine for hepatitis B reactivation in patients with aggressive lymphoma receiving chemotherapy. *Ann Hematol* 83: 270–275.
- Lee, G.W., Ryu, M.H., Lee, J.L., Oh, S., Kim, E., Lee, J.H., *et al.* (2003) The prophylactic use of lamivudine can maintain dose-intensity of adriamycin in hepatitis-B surface antigen (HBsAg)-positive patients with non-Hodgkin's lymphoma who receive cytotoxic chemotherapy. *J Korean Med Sci* 18: 849–854.
- Li, H.R., Huang, J.J., Guo, H.Q., Zhang, X., Xie, Y., Zhu, H.L., *et al.* (2011) Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy. *J Viral Hepat* 18: 877–883.
- Li, Y.H., He, Y.F., Jiang, W.Q., Wang, F.H., Lin, X.B., Zhang, L., *et al.* (2006) Lamivudine prophylaxis reduces the incidence and severity of hepatitis in hepatitis B virus carriers who receive chemotherapy for lymphoma. *Cancer* 106: 1320–1325.
- Liang, R.H., Lok, A.S., Lai, C.L., Chan, T.K., Todd, D. and Chiu, E.K. (1990) Hepatitis B infection in patients with lymphomas. *Hematol Oncol* 8: 261–270.
- Lim, L.L., Wai, C.T., Lee, Y.M., Kong, H.L., Lim, R., Koay, E., *et al.* (2002) Prophylactic lamivudine prevents hepatitis B reactivation in chemotherapy patients. *Aliment Pharmacol Ther* 16: 1939–1944.
- Lok, A.S. and McMahon, B.J. (2009) Chronic hepatitis B: update 2009. *Hepatology* 50: 661–662 (<http://www.aasld.org>).
- Loomba, R., Rowley, A., Wesley, R., Liang, T.J., Hoofnagle, J.H., Pucino, F., *et al.* (2008) Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 148: 519–528.
- Martyak, L.A., Taqavi, E. and Saab, S. (2008) Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis. *Liver Int* 28: 28–38.
- Maruyama, T., Iino, S., Koike, K., Yasuda, K. and Milich, D.R. (1993) Serology of acute exacerbation in chronic hepatitis B virus infection. *Gastroenterology* 105: 1141–1151.
- Matsue, K., Kimura, S., Takanashi, Y., Iwama, K., Fujiwara, H., Yamakura, M., *et al.* (2010) Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer* 116: 4769–4776.

- Mendez-Navarro, J., Corey, K.E., Zheng, H., Barlow, L.L., Jang, J.Y., Lin, W., *et al.* (2011) Hepatitis B screening, prophylaxis and re-activation in the era of rituximab-based chemotherapy. *Liver Int* 31: 330–339.
- Nagamatsu, H., Itano, S., Nagaoka, S., Akiyoshi, J., Matsugaki, S., Kurogi, J., *et al.* (2004) Prophylactic lamivudine administration prevents exacerbation of liver damage in HBe antigen positive patients with hepatocellular carcinoma undergoing transhepatic arterial infusion chemotherapy. *Am J Gastroenterol* 99: 2369–2375.
- Nagamatsu, H., Kumashiro, R., Itano, S., Matsugaki, S. and Sata, M. (2003) Investigation of associating factors in exacerbation of liver damage after chemotherapy in patients with HBV-related HCC. *Hepatol Res* 26: 293–301.
- Nair, P.V., Tong, M.J., Stevenson, D., Roskamp, D. and Boone, C. (1986) A pilot study on the effects of prednisolone withdrawal on serum hepatitis B virus DNA and HBeAg in chronic active hepatitis B. *Hepatology* 6: 1319–1324.
- Nakamura, Y., Motokura, T., Fujita, A., Yamashita, T. and Ogata, E. (1996) Severe hepatitis related to chemotherapy in hepatitis B virus carriers with hematologic malignancies. Survey in Japan, 1987–1991. *Cancer* 78: 2210–2215.
- Noterdaeme, T., Longree, L., Bataille, C., Deroover, A., Lamprove, A., Delwaide, J., *et al.* (2011) Liver transplantation for acute hepatic failure due to chemotherapy-induced HBV reactivation in lymphoma patients. *World J Gastroenterol* 17: 3069–3072.
- Ohtsu, T., Sai, T., Oka, M., Shgai, Y. and Tobinai, K. (1991) Activation of hepatitis B virus infection by chemotherapy containing glucocorticoid in hepatitis B virus carriers with hematologic malignancies. *Japan J Clin Oncol* 21: 360–365.
- Pelizzari, A.M., Motta, M., Cariani, E., Turconi, P., Borlenghi, E. and Rossi, G. (2004) Frequency of hepatitis B virus mutant in asymptomatic hepatitis B virus carriers receiving prophylactic lamivudine during chemotherapy for hematologic malignancies. *Hematol J* 5: 325–328.
- Perez-Roldan, F., Gonzalez-Carro, P. and Villafanez-Garcia, M.C. (2005) Adefovir dipivoxil for chemotherapy-induced activation of hepatitis B virus infection. *N Engl J Med* 352: 310–311.
- Persico, M., De Marino, F., Russo, G.D., Morante, A., Rotoli, B., Torella, R., *et al.* (2002) Efficacy of lamivudine to prevent hepatitis reactivation in hepatitis B virus-infected patients treated for non-Hodgkin lymphoma. *Blood* 99: 724–725.
- Pinto, P.C., Hu, E., Bernstein-Singer, M., Pinter-Brown, L. and Govindarajan, S. (1990) Acute hepatic injury after the withdrawal of immunosuppressive chemotherapy in patients with hepatitis B. *Cancer* 65: 878–884.
- Rossi, G., Pelizzari, A., Motta, M. and Puoti, M. (2001) Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. *Br J Haematol* 115: 58–62.
- Saab, S., Dong, M.H., Joseph, T.A. and Tong, M.J. (2007) Hepatitis B prophylaxis in patients undergoing chemotherapy for lymphoma: a decision analysis model. *Hepatology* 46: 1049–1056.
- Shibolet, O., Ilan, Y., Gillis, S., Hubert, A., Shouval, D. and Safadi, R. (2002) Lamivudine therapy for prevention of immunosuppressive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. *Blood* 100: 391–396.
- Sorrell, M.F., Belongia, E.A., Costa, J., Green, I.F., Grem, J.L., Inadomi, J.M., *et al.* (2009) National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology* 49: S4–S12.
- Steinberg, J.L., Yeo, W., Zhong, S., Chan, J.Y., Tam, J.S., Chan, P.K., *et al.* (2000) Hepatitis B virus reactivation in patients undergoing cytotoxic chemotherapy for solid tumours: precore/core mutations may play an important role. *J Med Virol* 60: 249–255.
- Sugimoto, R., Enjoji, M., Kotoh, K., Noguchi, K., Tsuruta, S., Nakamuta, M., *et al.* (2004) Effect of lamivudine for hepatitis B virus reactivation in blood cancer patients undergoing immunosuppressive chemotherapy. *Fukuoka Igaku Zasshi* 95: 274–279.
- Tsutsumi, Y., Shigematsu, A., Hashino, S., Tanaka, J., Chiba, K., Masauzi, N., *et al.* (2009) Analysis of reactivation of hepatitis B virus in the treatment of B cell non-Hodgkin's lymphoma in Hokkaido. *Ann Hematol* 88: 375–377.
- Vassiliadis, T., Garipidou, V., Tziomalos, K., Perifanis, V., Giouleme, O. and Vakalopoulou, S. (2005) Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic malignancies treated with chemotherapy – a prospective case series. *Am J Hematol* 80: 197–203.
- Wands, J.R., Chura, C.M., Roll, F.J. and Maddrey, W.C. (1975) Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* 68: 105–112.
- Weinbaum, C.M., Mast, E.E. and Ward, J.W. (2009) Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *Hepatology* 49: S35–S44.

- Xunrong, L., Yan, A.W., Liang, R. and Lau, G.K. (2001) Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy – pathogenesis and management. *Rev Med Virol* 11: 287–299.
- Yeo, W., Chan, P.K.S., Chan, H.L.Y., Mo, F.K.F. and Johnson, P.J. (2001) Hepatitis B virus reactivation during cytotoxic chemotherapy-enhanced viral replication precedes overt hepatitis. *J Med Virol* 65: 473–477.
- Yeo, W., Chan, P.K.S., Ho, W.M., Zee, B., Lam, K.C., Lei, K.I., *et al.* (2004a) Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 22: 927–934.
- Yeo, W., Chan, P.K.S., Hui, P., Ho, W.M., Lam, K.C., Kwan, W.H., *et al.* (2003) Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 70: 553–561.
- Yeo, W., Chan, T.C., Leung, N.W.Y., Lam, W.Y., Mo, F.K.F., Chu, M.T., *et al.* (2009) Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 27: 605–611.
- Yeo, W., Chan, P.K.S., Zhong, S., Ho, W.M., Steinberg, J.L., Tam, J.S., *et al.* (2000a) 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* 62: 299–307.
- Yeo, W., Ho, W.M., Hui, P., Chan, P.K., Lam, K.C., Lee, J.J., *et al.* (2004b) Use of lamivudine to prevent hepatitis B virus reactivation during chemotherapy in breast cancer patients. *Breast Cancer Res Treat* 88: 209–215.
- Yeo, W., Hui, E.P., Chan, A.T.C., Ho, W.M., Lam, K.C., Chan, P.K.S., *et al.* (2005) Prevention of hepatitis B virus reactivation in patients with nasopharyngeal carcinoma with lamivudine. *Am J Clin Oncol* 28: 379–384.
- Yeo, W., Lam, K.C., Zee, B., Chan, P.S.K., Mo, F.K.F., Ho, W.M., *et al.* (2004c) Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 15: 1661–1666.
- Yeo, W., Zee, B., Zhong, S., Chan, P.K.S., Wong, W.L., Ho, W.M., *et al.* (2004d) Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 90: 1306–1311.
- Yeo, W., Zhong, S., Chan, P.K., Ho, W.M., Wong, H.T., Chan, A.S., *et al.* (2000b) Sequence variations of precore/core and precore promoter regions of hepatitis B virus in patients with or without viral reactivation during cytotoxic chemotherapy. *J Viral Hepat* 7: 448–458.
- Yun, J., Kim, K.H., Kang, E.S., Gwak, G.Y., Choi, M.S., Lee, J.E., *et al.* (2011) Prophylactic use of lamivudine for hepatitis B exacerbation in post-operative breast cancer patients receiving anthracycline-based adjuvant chemotherapy. *Br J Cancer* 104: 559–563.
- Zhong, S., Yeo, W., Schroder, C., Chan, P.K., Wong, W.L., Ho, W.M., *et al.* (2004) 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* 11: 55–59.
- Ziakas, P.D., Karsaliakos, P. and Mylonakis, E. (2009) Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. *Haematologica* 94: 998–1005.