RESEARCH ARTICLE

Efficacy of Prophylactic Entecavir for Hepatitis B Virus-Related Hepatocellular Carcinoma Receiving Transcatheter Arterial Chemoembolization

Xing Li[1&], Xiang Zhong[2&], Zhan-Hong Chen[1&], Tian-Tian Wang[1], Xiao-Kun Ma[1], Yan-Fang Xing[3], Dong-Hao Wu[1], Min Dong[1], Jie Chen[1], Dan-Yun Ruan[1], Ze-Xiao Lin[1], Jing-Yun Wen[1], Li Wei[1], Xiang-Yuan Wu[1]*, Qu Lin[1]*

Abstract

<u>Background and Aims:</u> Hepatitis B virus (HBV) reactivation was reported to be induced by transcatheter arterial chemoembolization (TACE) in HBV-related hepatocellular carcinonma (HCC) patients with a high incidence. The effective strategy to reduce hepatitis flares due to HBV reactivation in this specific group of patients was limited to lamivudine. This retrospective study was aimed to investigate the efficacy of prophylactic entecavir in HCC patients receiving TACE. <u>Methods:</u> A consecutive series of 191 HBV-related HCC patients receiving TACE were analyzed including 44 patients received prophylactic entecavir. Virologic events, defined as an increase in serum HBV DNA level to more than 1 log10 copies/ml higher than nadir the level, and hepatitis flares due to HBV reactivation were the main endpoints. <u>Results:</u> Patients with or without prophylactic were similar in host factors and the majorities of characteristics regarding to tumor factors, HBV status, liver function and LMR. Notably, cycles of TACE were parallel between the groups. Ten (22.7%) patients receiving prophylactic entecavir reached virologic response. The patients receiving prophylactic entecavir presented significantly reduced virologic events (6.8% vs 54.4%, p=0.000) and hepatitis flares due to HBV reactivation (0.0% vs 11.6%, p=0.039) compared with patients without prophylaxis. Kaplan-Meier analysis illustrated that the patients in the entecavir group presented significantly improved virologic events free survival (p=0.000) and hepatitis flare free survival (p=0.017). Female and Eastern Cooperative Oncology Group (ECOG) performance status 2 was the only significant predictors for virological events in patients without prophylactic antiviral. Rescue antiviral therapy did not reduce the incidence of hepatitis flares due to HBV reactivation. <u>Conclusion:</u> Prophylactic entecavir presented promising efficacy in HBV-related cancer patients receiving TACE. Lower performance status and female gender might be the predictors for HBV reactivation in these patients.
Keywords: Hepatitis B virus - hepatocellular carcinoma - transcatheter arterial chemoembolization - hepatitis flare

Introduction

Hepatitis B virus (HBV) reactivation in patients receiving systemic chemotherapy has been profoundly investigated in recent years (Li et al., 2010; Torres and Davila, 2012; Wu et al., 2013; Yeo and Chan, 2013; Li et al., 2014). However, it has not been fully evaluated in HBV-related hepatocellular carcinonma (HCC) patients receiving Transcatheter arterial chemoembolization (TACE) due to limited sample size and amount of studies (Vizzini et al., 2003; Jang et al., 2004; Park et al., 2005; Jang et al., 2006; Peng et al., 2012). TACE is an local invasive chemotherapy to tumor lesion and the surrounding normal liver tissue, both of which is highly associated with chronic HBV infection (Liver, 2012; Arzumanyan et al., 2013). This feature indicated the

distinction of HBV reactivation in HCC patients receiving TACE with those developing among patients receiving systematic chemotherapy for other maligancies. Thus, it is imperative to identify the unique characteristics of HBV reactivation induced by TACE among HCC patients.

HBV reactivation was reported to be induced by TACE in HBV-related HCC patients with a high incidence (Jang et al., 2004; Jang et al., 2006; Peng et al., 2012). The effective strategy to reduce hepatitis flares due to HBV reactivation for HCC patients receiving TACE was limited to lamivudine (Nagamatsu et al., 2004; Jang et al., 2006). However, according to recent studies including ours, prophylactic lamivudine presented a high incidence of virus resistance, which caused consequent virus breakthrough and hepatitis flares (Hongthanakorn et al., 2011; Kim et al., 2012; Wu et al., 2013). Thus, it

*[1]Department of Medical Oncology, the Third Affiliated Hospital of Sun Yat-sen University, [3]Department of Nephrology, the Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, [2]Department of Medical Oncology, Shenzhen People's Hospital, Shenzhen, China &Equal contributors *For correspondence: wuxiangy@mail.sysu.edu.cn; gzliqu@163.com*

is appropriate to avoid lamivudine and to use the drugs associated with a low incidence of resistance, such as entecavir, as first-line prophylactic agents, since HCC patients receiving TACE probably need prolonged anti-HBV therapy (over 12 months). And, in our center of HCC, entecavir was increasingly administrated to HCC patients receiving TACE as a prophylaxis for HBV reactivation.

Thus, this retrospective study was carried out to identify the unique characteristics of HBV reactivation induced by TACE among HCC patients, and further to investigate the efficacy of prophylactic entecavir in HCC patients receiving TACE. Furthermore, we intended to access the incidence of entecavir resistance.

Materials and Methods

The patients

During the period between September 2009 and September 2012, we investigated a consecutive series of 191 HBV related HCC patients receiving TACE in the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. The diagnosis of HCC was confirmed by pathology or the American Association for the study of liver diseases radiological criteria by either computed tomography (CT) or magnetic resonance imaging (MRI) (Bruix and Sherman, 2011). TACE was given to HCC patients staged between Barcelona Clinic liver cancer (BCLC) stages A4 to C according to the experience of the interventional radiologists in charge. Prophylactic entecavir was administrated before the first cycle of TACE in 44 patients according to the view of the interventional radiologists in charge and the compliance of patients. Accordingly, patients were divided into two groups: the control group without prophylaxis and the entecavir group.

All patients were screened for serological hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb) and HBV DNA on a routine basis. Routine liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and international normalized ratio (INR) as well as serum HBV DNA were assessed a day prior to the commencement of each TACE cycle. The blood test was repeated at 4- to 6-week interval until the last day of follow up after completion of TACE or death of the patients.

Tests for serum HBV DNA and routine liver function tests were carried out once the patients were admitted to our hospital for treatment of HBV DNA rise or ALT elevation. All patients were also screened for serum human immunodeficiency virus (HIV) antibody, hepatitis A virus (HAV) antibody, hepatitis C virus (HCV) antibody, hepatitis D virus (HDV) antigen, HDV antibody, and hepatitis E virus (HEV) antibody. Patients who were positive for HIV, those with other types of hepatitis virus infection except HBV, those who were pregnant before diagnosis and patients received systematic chemotherapy were excluded from this study. This study was approved by the Clinical Ethics Review Board at both the Third Affiliated Hospital of Sun Yat-sen University. A written informed consent was obtained from all the patients at the time of admission.

Definitions

Virologic events for patients without prophylaxis were defined as an increase in serum HBV DNA level to more than 1 log10 IU/ml higher than the level before TACE was initiated (Wu et al., 2013). Responsiveness to entecavir was defined in compliance with the European Association for the Study of the Liver (EASL) clinical practice guidelines and the Association for the Study of Liver Diseases (ASLD) practice guidelines on chronic hepatitis B (Lok and McMahon, 2007; Lok and McMahon, 2009; Liver, 2012). Virologic events for patients with prophylaxis, was referred to a rise in serum HBV DNA to the extent of 1 log10 (tenfold) above nadir after achieving virologic response. Patients with circulating HBeAb and without detectable HBeAg who remained or became HBV DNA positive were presumed to possess precore mutation. The definition of hepatitis flares due to HBV reactivation was at least threefold of ALT that exceeded the upper limit of normal range or an absolute increase of ALT to more than 100 U/l when compared with the baseline value accompanied by viral breakthrough or virologic events (Wu et al., 2013). Rescue antiviral therapy were defined as administration of nucleoside analogues (NUCs) to patients without prophylactic agents when virologic events or hepatitis flare due to HBV reactivations were confirmed.

Patient follow up and statistical analysis

Patients returned for follow-up appointments at 4- to 6-week interval until the last day of follow up after completion of TACE or death of the patients. The follow-up duration was calculated from the first day of TACE to the day of death, or to the last examination. The median follow-up time was 43.9 weeks (range, 1.0 weeks-164.0 weeks) for the control group and 59.1 weeks (range, 3.0 weeks-131.0 weeks) for the entecavir group. The following endpoints were assessed: virologic events free survival and hepatitis flare free survival. We calculated virologic events free survival from the first day of treatment to the date of detected virologic events, and hepatitis flare free survival was calculated from the first day of treatment to the date of detection of hepatitis B flares due to HBV reactivation, respectively.

Statistical differences in clinical characteristics between two groups analyzed were compared using the Mann-Whitney, chi-square, and Fisher's exact tests. Multivariate analysis using a Cox proportional hazards model was used to test for independent significance by backward elimination of insignificant baseline characteristics and explanatory variables. The primary endpoint of this study was the development of HBV reactivation. The difference of HBV reactivation incidence between patients with or without prophylactic entecavir was determined by Kaplan-Meier analysis. Covariates including host factors (ie, age and gender), tumor factors (ie, diameters of main lesions and N classification), HBV status (ie, HBeAg and baseline HBV DNA), liver function (ie, alanine transaminase and Child-Turcotte-Pugh score), cycles of TACE and immune function (ie, peripheral blood lymphocyte/monocyte ratio, LMR) were included in all tests. All values quoted were two-sided and a P<0.05

was considered to be statistically significant. Statistical analyses were performed using SPSS V. 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

Patients with or without prophylactic were similar in host factors and the majorities of characteristics regarding to tumor factors, HBV status, liver function and LMR. Notably, cycles of TACE were parallel between the groups. However, patients administrated with prophylactic entecavir presented smaller tumor lensions, reduced Child-Turcotte-Pugh score and higher baseline HBV DNA (Table 1).

Differences in clinical outcomes between patients with or without prophylactic entecarvir

10 (22.7%) patients receiving prophylactic entecavir achieved HBV DNA drop to undetectable level (<100IU/ml). The patients receiving prophylactic entecavir presented significantly reduced virologic events (6.8% vs 54.4%, p=0.000) and hepatitis flares due to HBV reactivation (0.0% vs 11.6%, p=0.039) compared with patients without prophylaxis (Table 1). Furthermore, Kaplan-Meier analysis illustrated that the patients in the entecavir group presented significantly improved virologic events free survival (p=0.000) and hepatitis flare free survival (p=0.017) (Figure 1).

In order to determine influence of baseline characteristics on the outcome of prophylactic entecavir, especially for those differing between the groups, multivariate analysis using a Cox proportional hazards model was used for independent significance by backward elimination. It revealed that gender and Eastern Cooperative Oncology Group (ECOG) performance status were the only significant variable associated with virologic events, which were parallel between the entecavir group and the control group. And, none of the characteristics that were different between the groups influenced the outcome of prophylactic entecavir (Table 2).

Table 1. Characteristics of Patients in the Control Group and the Entecavir Group

Characteristics	Control group n=147	Entecavir Group n=44	*P*
Age (years, range)	53.3 (11.0-84.0)	51.0 (28-85)	0.770
Sex (n, %)			0.393
Male	132 (89.8%)	42 (95.5%)	
Female	15 (10.2%)	2 (4.5%)	
ECOG Performance Status (n, %)			0.966
0-1	124 (84.4%)	37 (84.1%)	
2	23 (15.6%)	7 (15/9%)	
HBeAg (n, %)	19 (12.9%)	11 (25.0%)	0.053
Baseline HBV DNA (log10) (IU/ml)	<2.0 (<2.0-8.0)	5.0 (<2.0-8.0)	0.000
Tumor number (n, %)			0.952
1	131 (89.1%)	40 (90.9%)	
>1	16 (10.9%)	4 (9.1%)	
Longest diameter of main lesion (mm)	87.0 (11.0-212.0)	64.0 (11.0-143.0)	0.038
N stage (n, %)	19 (12.9%)	7 (15.9%)	0.613
M stage (n, %)	11 (7.5%)	3 (6.8%)	1.000
Portal invasion (n, %)	72 (49.0%)	18 (40.9%)	0.347
AFP (ng/ml) (n, %)			0.284
<400	70 (47.6%)	25 (56.8%)	
>400	77 (52.4%))	19 (43.2%)	
ALT (IU/l)	45 (9-290)	48 (10-135)	0.900
AST (IU/l)	59 (12-931)	57.5 (15-190)	0.985
Albumin (g/l)	39.9 (22.5-51.0)	37.5 (23.0-53.3)	0.007
GGT (IU/l)	131 (21-938)	126.5 (17-1136)	0.647
Alkaline phosphatase (IU/l)	114 (44-1048)	105 (50-308)	0.216
Total bilirubin (mmol/L)	16.1 (5.6-62.8)	18.3 (5.2-84.4)	0.173
Bilirubin direct (mmol/L)	5.1 (1.3-39.5)	5.9 (2.6-40.9)	0.191
INR median (median, range)	1.04 (0.84-1.64)	1.13 (0.88-1.49)	0.000
Child-Pugh score (n, %)			0.011
A	130 (88.4%)	32 (72.7%)	
B	17 (11.6%)	12 (27.3%)	
LMR (median, range)	3.13 (0.36-39.25)	3.49 (0.54-7.89)	0.474
TACE cycles	2 (1-8)	2 (1-6)	0.277
Virological Event (n, %)	80 (54.4%)	3 (6.8%)	0.000
Hepatitis B flares* (n, %)	17 (11.6%)	0 (0.0%)	0.039

*Hepatitis B flares due to HBV reactivation. Abbreviation: ECOG, Eastern Cooperative Oncology Group; HBeAg, hepatitis B e antigen; HBV Hepatitis B virus; AFP a-fetoprotein; ALT alanine aminotransferase; AST, aspartate aminotransferase; CCT, Gamma-glutamyl transpeptidase; INR, International normalized ratio; LMR, lymphocyte/monocyte ratio; TACE, transcatheter arterial chemoembolization. P-values were calculated using the Mann-Whitney test, chi-square test or Fisher exact test if indicated
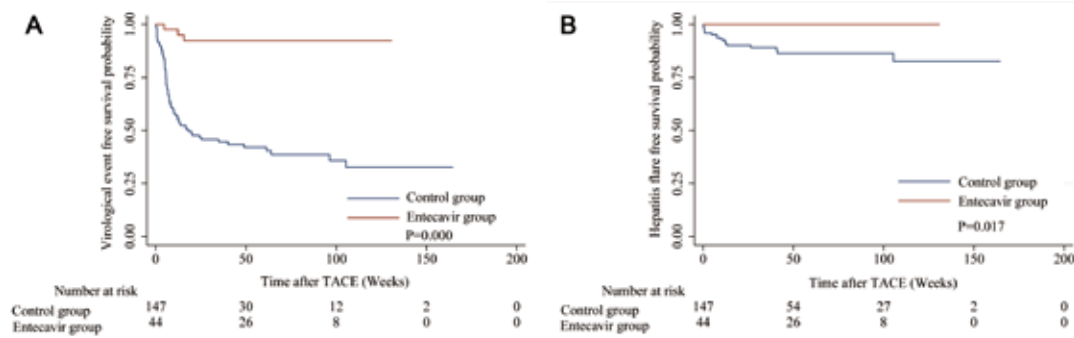
Figure 1. Kaplan-Meier Analysis of Patients with or Without Prophylactic Entecavir. A) virologic events free survival; **B)** hepatitis flare free survival

Table 2. Multivariate Analysis of the Association between Baseline Characteristics and Virological Events Free Survival

Characteristics	P	HR	95% CI for HR
Sex	0.022	0.495	0.217-0.903
ECOG Performance Status	0.023	1.905	1.092-3.325

*Abbreviation: ECOG, Eastern Cooperative Oncology Group; 95% CI 95% confidence interval; HR, hazards ratio. P-values were calculated using the multivariate Cox proportional hazards model by backward elimination

Table 3. Multivariate Analysis of the Predictors of Virological Events in the Control Group

Characteristics	P	HR	95% CI for HR
Sex	0.045	0.528	0.283-0.985
ECOG Performance Status	0.014	2.024	1.155-3.546

*Abbreviation: ECOG, Eastern Cooperative Oncology Group; 95% CI 95% confidence interval; HR, hazards ratio. P-values were calculated using the multivariate Cox proportional hazards model by backward elimination

Table 4. Outcome of the Patients Presented Virological Event

Outcome	Observe n=59	Rescue n=21	P
Hepatitis flare*	10 (16.9%)	7 (33.3%)	0.169
Death	2 (3.4%)	0 (0.0%)	1.000

*Hepatitis B flares due to HBV reactivation. P-values were calculated using the chi-square test or Fisher exact test if indicated

Predictors of virologic events and HBV Reactivation in patients without prophylactic antiviral

As high as 54.4% patients without prophylactic entecavir developed confirmed HBV DNA elevation. Multivariate analysis using a Cox proportional hazards model using backward elimination identified that female and ECOG performance score 2 was the only significant predictors for virological events in patients without prophylactic antiviral (Table 3).

Outcome of virologic events and the efficacy of rescue antiviral therapy

80 patients developed virologic events due to lack of prophylaxis with another 3 developing virus breakthrough. Based on the experience of the interventional radiologists in charge, NUCs were administrated to 21 patients without prophylactic agents when virologic events or hepatitis flare

due to HBV reactivations were confirmed with the rest received observation due to financial causes. However, rescue antiviral therapy did not reduce the incidence of hepatitis flares due to HBV reactivation compared with observation (33.3% vs 16.9%, *p*=0.169). (Table 4)

Discussion

It is universally advised that patients with chronic hepatitis B virus (HBV) infection should receive prophylactic antiviral before commence of chemotherapy (Liver, 2012; Torres and Davila, 2012; Yeo and Chan, 2013). Current clinical guidelines recommended entecavir as a preferable agent among all the prophylactic NUCs for its high antiviral potential and strong resistance barrier (Lok and McMahon, 2007; Lok and McMahon, 2009; Liver, 2012). However, the majority of evidence was based on the studies of prophylactic lamivudine (Ziakas et al., 2009), entecavir was only tested recently in lymphoma patients (Huang et al., 2014). Likewise, the high incidence of HBV reactivation and its latent risk in HBV related HCC patients receiving TACE were reported previously (Jang et al., 2006; Jang et al., 2011) and the potential of prophylactic lamivudine were presented in a clinical trial (Jang et al., 2006), with the efficacy of prophylactic entecavir still undetermined. In this study, we firstly reported the efficacy of prophylactic entecavir. For HBV related HCC patients receiving TACE, prophylactic entecavir significantly reduced virologic events (6.8% vs 54.4%, *p*=0.000) and hepatitis flares due to HBV reactivation (0.0% vs 11.6%, *p*=0.039). Thus, entecavir was an effective prophylaxis to HBV reactivation in HCC patients receiving TACE.

The endpoint of antiviral prophylaxis should be designed based on the nature history of HBV reactivation (McMahon, 2009; Li et al., 2012; Wu et al., 2013). HBV reactivation consisted of at least two stages: increase of viral replication and hepatitis flares (Torres and Davila, 2012; Wu et al., 2013). As we have reported (Wu et al., 2013), antiviral therapy targeted at the increase of HBV DNA was more effective than those targeted at hepatitis flares. Thus, virologic events were assigned as the primary endpoint in this study. Regarding this, entecavir presented a nearly 90% reduction of virological events, which finally leaded to an deceased incidence of hepatitis flares. Thus, virologic events might be a more preferable endpoint for future studies regarding HBV reactivation.

The baseline characteristics of the control group and the entecavir group were not consistent in all the aspects, which was a weakness of our study. Patients in entecavir group presented smaller tumor burden and severe HBV associated variables, which indicated their relatively better prognosis regarding malignancy and severe liver disease background. These patients were presumed to be more vulnerable to HBV reactivation. But, this bias of entecavir prescription did not influence the efficacy of entecavir. According to the multivariate analysis, all the inconsistent characteristics did not associate the incidence of virological events.

Rescue antiviral therapy was another option as the prophylaxis of HBV reactivation. However, according to our previous study (Wu et al., 2013), it's efficacy relied the timing of administration, that was administrating antiviral agents when the increase of HBV DNA were confirmed and ALT were not elevated. Due to the difficulty in the intensity of HBV DNA monitoring, rescue antiviral therapy was abandoned in patients receiving systematic chemotherapy. Likewise, rescue antiviral therapy displayed unacceptable efficacy as prophylaxis in patients receiving TACE in this study, which further reinforce the essentiality of prophylactic entecavir.

Our study identified male gender and good performance status as protective factors for virologic events both in patients without prophylaxis. Previous studies reported that HBV DNA load were the predictor for HBV reactivation in HBV-related HCC patients receiving TACE (Zhong et al., 2004; Jang et al., 2006; Jang et al., 2011). However, the mechanism of HBV reactivation did not only rely on the virus behavior but also the background of host. Our results firstly indicated the significant influence of host background on the biological behavior of HBV and the uniqueness of HBV reactivation in this group of patients. Consequently, female patients with relatively lower performance status shall be put extra attention on in respect of HBV reactivation.

In summary, this study identified the efficacy the prophylactic entecavir in HBV-related cancer patients receiving TACE. Lower performance status and female gender might be the predictor for HBV reactivation in these patients.

Acknowledgements

References

Arzumanyan A, Reis HM, Feitelson MA (2013). Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer*, **13**, 123-35.

Bruix J, Sherman M (2011). Management of hepatocellular carcinoma: an update. *Hepatol*, **53**, 1020-2.

Hongthanakorn C, Chotiyaputta W, Oberhelman K, et al (2011). Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos (t)ide analogues in clinical practice. *Hepatol*, **53**, 1854-63.

Huang H, Li X, Zhu J, et al (2014). Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA*, **312**, 2521-30.

Jang JW, Choi JY, Bae SH, et al (2004). Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. *J Hepatol*, **41**, 427-35.

Jang JW, Choi JY, Bae SH, et al (2006). A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology*, **43**, 233-40.

Jang JW, Kwon JH, You CR, et al (2011). Risk of HBV reactivation according to viral status and treatment intensity in patients with hepatocellular carcinoma. *Antivir Ther*, **16**, 969-77.

Kim IK, Kim BG, Kim W, et al (2012). Clinical prediction of failure of Lamivudine prophylaxis for hepatitis B virus-infected patients undergoing cytotoxic chemotherapy for malignancy. *Antimicrob Agents Chemother*, **56**, 5511-9.

Li X, Lin Q, Dong M, et al (2010). Prognostic analysis of acute exacerbations of hepatitis-B after chemotherapy in combination with rituximab in 19 patients with lymphoma. *Leuk Lymphoma*, **51**, 1678-85.

Li X, Xing YF, Lin Q, et al (2012). The treatment of severe hepatitis B virus reactivation after chemotherapy. *Nat Rev Clin Oncol*, **9**, 350.

Li X, Zhong X, Chen ZH, et al (2014). Hepatitis B virus DNA negativity acts as a favorable prognostic factor in hepatocellular carcinoma patients. *Asian Pac J Cancer Prev*, **15**, 9635-41.

Liver EAftSot (2012). EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol*, **57**, 167-85.

Lok AS, McMahon BJ (2007). Chronic hepatitis B. *Hepatol*, **45**, 507-39.

Lok AS, McMahon BJ (2009). Chronic hepatitis B: update 2009. *Hepatol*, **50**, 661-2.

McMahon BJ (2009). The natural history of chronic hepatitis B virus infection. *Hepatol*, **49**, 45-55.

Nagamatsu H, Itano S, Nagaoka S, 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**, 2369-75.

Park JW, Park KW, Cho SH, et al (2005). Risk of hepatitis B exacerbation is low after transcatheter arterial chemoembolization therapy for patients with HBV-related hepatocellular carcinoma: report of a prospective study. *Am J Gastroenterol*, **100**, 2194-200.

Peng JW, Lin GN, Xiao JJ, et al (2012). Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. *Asia Pac J Clin Oncol*, **8**, 356-61.

Torres HA, Davila M (2012). Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol*, **9**, 156-66.

Vizzini GB, Luca A, Marino IR (2003). Hepatitis B virus reactivation after a single session of transarterial chemoembolization in patients with hepatocellular carcinoma. *Ann Intern Med*, **138**, 691-2.

Wu XY, Li X, Chen ZH, et al (2013). An optimized antiviral

modification strategy for prevention of hepatitis B reactivation in patients undergoing prophylactic lamivudine and chemotherapy: a pilot study. Tumour Biol, 34, 909-18.

Yeo W, Chan HL (2013). Hepatitis B virus reactivation associated with anti-neoplastic therapy. *J Gastroenterol Hepatol*, **28**, 31-7.

Zhong S, Yeo W, Schroder C, 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**, 55-9.

Ziakas PD, Karsaliakos P, 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.