RESEARCH ARTICLE

Hepatitis B Virus DNA Negativity Acts as a Favorable Prognostic Factor in Hepatocellular Carcinoma Patients

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Abstract

Background: This retrospective study was aimed to investigate the efficacy of prophylactic agents in hepatocellular carcinoma (HCC) patients receiving TACE and compare the difference between lamivudine and entecavir. Materials and Methods: A consecutive series of 203 HBV-related HCC patients receiving TACE were analyzed including 91 patients given prophylactic agents. Virologic events, defined as an increase in serum HBV DNA level to more than 1 log10 IU/ml higher than the nadir level, hepatitis flares due to HBV reactivation and progression free survival (PFS) were the main endpoints. Results: Some 48 (69.6%) reached virologic response. Prophylaxis significantly reduced virologic events (8.8% *vs* 58.0%, *p*=0.000) and hepatitis flares (1.1% *vs* 13.4%, *p*=0.001). Patients presenting undetectable HBV DNA levels displayed a significantly improved PFS as compared to those who never achieved undetectable HBV DNA. Prophylaxis and e-antigen positivity were the only significant variables associated with virologic events. In addition, prophylaxis was the only independent protective factor for hepatitis flares. Liver cirrhosis, more cycles of TACE, HBV DNA negativity, a lower Cancer of the Liver Italian Program score, non-metastasis and no hepatitis flares were protective factors for PFS. Prophylactic lamivudine demonstrated similar efficacy as entecavir. Conclusions: Prophylactic agents are efficacious for prevention of HBV reactivation in HCC patients receiving TACE. Achievement of undetectable HBV DNA levels displayed a significant capability in improving PFS. Moreover, persistent tumor residual lesions, positive HBV DNA and hepatitis B flares might be causes of tumor progression in these patients.

Keywords: Hepatitis B virus - hepatocellular carcinoma - transcatheter arterial chemoembolization - prognostic analysis

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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). HBV reactivation was reported to be induced by transcatheter arterial chemoembolization (TACE) in HBV-related hepatocellular carcinonma (HCC) patients with a high incidence (Jang et al., 2004; Jang et al., 2006; Lao et al., 2013). The effective strategy to reduce hepatitis flares due to HBV reactivation for HCC patients receiving TACE was limited to lamivudine (Jang et al., 2006; Lao et al., 2013). However, according to recent studies including ours, prophylactic lamivudine presented a high incidence of virus resistance, which caused consequent virus breakthrough and hepatitis flares (Kim et al., 2012; Wu et al., 2013). Thus, it is appropriate to evaluated nucleoside analogues (NUCs) 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). Besides, previous studies indicated that NUCs are effective in reduce tumor recurrence after radical surgery for patients with early stages of HCC (Lok and McMahon, 2009). However, the efficacy of NUCs on tumor control for HCC patients receiving TACE was not investigated.

TACE is acknowledged universally as an effective local therapy for HCC patients who are not suitable to radical surgery (Murata et al., 2013). However, there is little consensus on many details of the practical procedure, such as timing of repetitive TACE, efficacy evaluation, compounded therapy, and frequency of imaging surveillance (Li et al., 2013a; Wang et al., 2013). Differences in etiology of HCC, health insurance policy, experience of different centers might be the latent causes. Importantly, the baseline prognostic factors of HCC patients receiving TACE have not been clearly illustrated yet.

In our center of HCC in south china, TACE has become

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a routine procedure for HCC patients in last decades. And, NUCs, mainly entecavir and lamivudine, were increasingly administrated to HCC patients receiving TACE as a prophylaxis for HBV reactivation. Thus, this retrospective study was carried out to identify the efficacy of prophylactic antiviral on prevention of HBV reactivation and tumor control for HCC patients receiving TACE and the prognostic factors for these patients.

Materials and Methods

Patients

During the period between September 2009 and September 2012, we investigated a consecutive series of 203 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). TACE was given to HCC patients who were not amendable to or rejected radical surgery. And TACE was repeated as necessary based on follow-up CT scan indicating active tumor region. CT scan was performed every at 4- to 6-week interval for patients with potential active tumor lesion and at 8- to 12-week interval for patients reached complete response (CR). Prophylactic NUCs was administrated before the first cycle of TACE in 91 patients according to the view of the interventional radiologists in charge and the compliance of patients. Among them, 15 patients were given NUCs before diagnosis of HCC as a treatment to hepatitis B. 30, 46 and 14 patients received lamivudine, entecavir and adefovir, respectively. 1 patient was given lamivudine and adefovir. Accordingly, patients were divided into two groups: the control group without prophylaxis and the prophylactic 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. Responsiveness to prophylactic NUCs was defined in compliance with the European Association for the Study of the Liver (EASL) clinical practice guidelines (Liver, 2012). Virologic response was defined as a drop in the serum HBV DNA to undetectable levels by polymerase chain reaction (PCR) assays (<100IU/ml). Virologic event for patients with prophylaxis was referred to a rise in serum HBV DNA to the extent of 1 log10 (tenfold) above nadir after initiating of prophylaxis. 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 IU/ml when compared with the baseline value accompanied by or following virologic events.

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 11.52 months (range, 0.3 month-47.53 months) for the control group and 14.17 months (range, 0.1 months-43.00 months) for the prophylaxis group. The following endpoints were assessed: virologic events survival, hepatitis flare survival and progression free survival (PFS) (Lencioni and Llovet, 2010). PFS was calculated from the first day of treatment to the date of disease progression or death from any cause. We calculated virologic events survival from the first day of treatment to the date of detected virologic events, and hepatitis flare 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 NUCs was determined by Kaplan-Meier analysis. Covariates including host factors (ie, age and gender), Cancer of the Liver Italian Program (CLIP) score, tumor factors (ie, N and M classification), HBV status (ie, HBeAg and baseline HBV DNA), liver function (ie, ALT and liver cirrhosis), cycles of TACE 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 of HCC patients with or without prophylactic NUCs

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

Differences in clinical outcomes between patients with or without prophylactic NUCs

Among the 69 patients in prophylactic group with positive HBV DNA tests before TACE, 48 (69.6%) reached virologic response. The patients receiving prophylactic NUCs presented significantly reduced virologic events (8.8% *vs* 58.0%, p=0.000) and hepatitis

Table 1. Baseline Characteristics and Clinical Outcome of Patients in the Control Group and the Prophylaxis Group

Characteristics	Control Group n=112	Prophylactic Group n=91	p-value
Age (years, range)	53.9 (11.0-84.0)	52.7 (28.0-85.0)	0.698
Sex (n, %)			0.596
Male	101 (90.2%)	84 (92.3%)	
Female	11 (9.8%)	7 (7.7%)	
Liver cirrhosis (n, %)	88 (78.6%)	78 (85.7%)	0.190
ECOG Performance Status (n, %)			0.605
0-1	93 (83.0%)	73 (80.2%)	
2	19 (17.0%)	18 (19.8%)	
HBeAg (n, %)	16 (14.3%)	25 (27.5%)	0.020
Baseline HBV DNA (log10) (IU/ml)	<2.0 (<2.0-8.45)	4.57 (<2.0-7.94)	0.000
Tumor number (n, %)			0.316
1	99 (88.4%)	76 (83.5%)	
>1	13 (11.6%)	15 (16.5%)	
CLIP- morphology (n, %)	87.0 (11.0-212.0)	64.0 (11.0-143.0)	0.014
0	49 (43.8%)	52 (57.1%)	
1	9 (8.0%)	13 (14.3%)	
2	54 (48.2%)	26 (28.6%)	
N stage (n, %)	13 (11.6%)	9 (9.9%)	0.696
M stage (n, %)	10 (8.9%)	6 (6.6%)	0.539
Portal invasion (n, %)	50 (44.6%)	35 (38.5%)	0.375
AFP (ng/ml) (n, %)			0.061
<400	58 (51.8%)	59 (64.8%)	
>400	54 (48.2%)	32 (35.2%)	
ALT (IU/l)	42 (9-290)	45 (10-153)	0.835
AST (IU/l)	53 (19-931)	49 (15-325)	0.965
Albumin (g/l)	39.0 (22.0-51.0)	37.6 (23.0-53.3)	0.014
GGT (IU/l)	119 (21-938)	98 (17-1136)	0.384
Alkaline phosphatase (IU/l)	106 (44-1048)	103 (35-331)	0.595
Total bilirubin (mmol/L)	15.45 (5.6-62.8)	18.3 (4.7-109.8)	0.084
Fibrinogen (g/L)	3.32 (1.26-9.39)	2.95 (1.47-6.47)	0.001
INR median (median, range)	1.05 (0.84-2.03)	1.12 (0.77-2.21)	0.000
TACE cycles (median, range)	2 (1-7)	2 (1-6)	0.145
CLIP score (n, %)			0.495
0	22 (19.6%)	25 (27.5%)	
1	24 (21.4%)	23 (25.3%)	
2	19 (17.0%)	14 (15.4%)	
3	17 (15.2%)	11 (12.1%)	
4	25 (22.3%)	14 (15.4%)	
5	3 (2.7%)	4 (4.4%)	
6	2 (1.8%)	0 (0.0%)	
Child-Pugh score (n, %)			0.025
A	96 85.7%)	65 (71.4%)	
B	13 (11.6%)	24 (26.4%)	
C	3 (2.7%)	2 (2.2%)	
Clinical outcome			
HBV DNA negativity (n, %)	72 (64.3%)	69 (75.8%)	0.076
Virological Event (n, %)	65 (58.0%)	8 (8.8%)	0.000
Hepatitis B flares* (n, %)	15 (13.4%)	1 (1.1%)	0.001

* Hepatitis B flares due to HBV reactivation. Abbreviation: ECOG, Eastern Cooperative Oncology Group; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; CLIP, Cancer of the Liver Italian Program; AFP, a-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; INR, International normalized ratio; TACE, transcatheter arterial chemoembolization. *P*-values were calculated using the Mann-Whitney test, chi-square test or Fisher exact test if indicated

Table 2. Multivariate Analysis of the Independent Predictive Factors for PFS, Virologic Response and Hepatitis B Flares

Characteristics	*p*-value	HR	95% CI for HR	
PFS				
Liver cirrhosis	0.044	0.618	0.387	0.986
CLIP score	0.003	1.219	1.070	1.388
N stage	0.007	2.253	1.247	4.070
M stage	0.003	2.858	1.421	5.750
Cycles of TACE	0.000	1.233	1.098	1.384
HBV DNA negative	0.000	0.475	0.323	0.697
Hepatitis flares	0.036	1.891	1.042	3.431
GGT	0.025	1.001	1.000	1.002
Virologic events				
Prophylactic NUCs	0.000	0.068	0.031	0.148
HBeAg positive	0.006	2.251	1.266	4.004
Hepatitis B flares				
Prophylactic NUCs	0.011	0.057	0.006	0.517

*Abbreviation: PFS, progression free survival; ECOG, Eastern Cooperative Oncology Group; 95% CI, 95% confidence interval; HR, hazards ratio; CLIP, Cancer of the Liver Italian Program; TACE, transcatheter arterial chemoembolization; HBV, hepatitis B virus; GGT, γ-glutamyl transpeptidase; NUCs, nucleoside analogues; HBeAg, hepatitis B e antigen. P-values were calculated using the multivariate Cox proportional hazards model by backward elimination

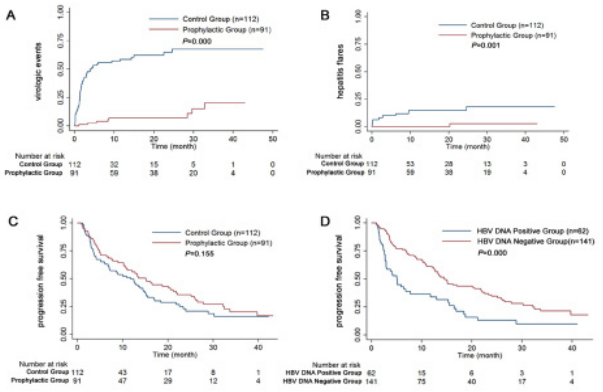

Figure 1. Kaplan-Meier analysis for HCC Patients Receiving TACE with or Without Antiviral Agents. Kaplan-Meier failure curves are shown for **A)** virologic events and **B)** hepatitis flares in HCC patients receiving TACE in control group and prophylaxis group. Kaplan-Meier survival curves for progression free survival in HCC patients receiving TACE in control group and prophylaxis group **C)** and in patients achieved undetectable HBV DNA level (HBV DNA negative group) or not (HBV DNA positive group) **D)** P values were calculated using the unadjusted log-rank test. Abbreviation: HCC, hepatocellular carcinonma; TACE, transcatheter arterial chemoembolization; HBV, hepatitis B virus

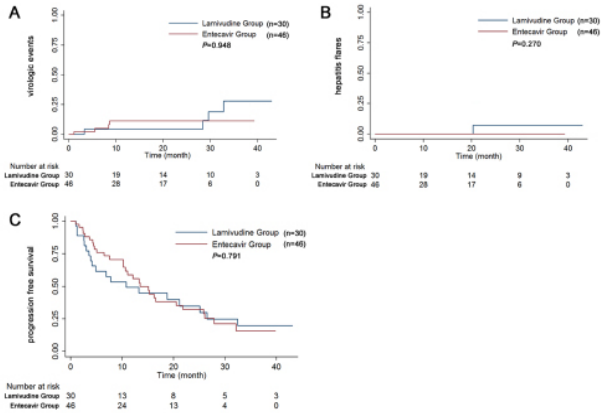

Figure 2. Kaplan-Meier analysis for HCC Patients Receiving TACE with Prophylactic Lamivudine or Entecavir. Kaplan-Meier failure curves are shown for **A)** virologic events and **B)** hepatitis flares in HCC patients receiving TACE in lamivudine group and entecavir group. Kaplan-Meier survival curves for progression free survival in HCC patients receiving TACE in lamivudine group and entecavir group **C)** P values were calculated using the unadjusted log-rank test. Abbreviation: HCC, hepatocellular carcinonma; TACE, transcatheter arterial chemoembolization

flares due to HBV reactivation (1.1% *vs* 13.4%, p=0.001) compared with patients without prophylaxis (Table 1). Furthermore, Kaplan-Meier analysis illustrated that the patients in the prophylactic group presented significantly improved virologic events (p=0.000) and hepatitis flare free (p=0.001) (Figure 1A and 1B).

Furthermore, the influence of prophylactic NUCs on PFS were analyzed by Kaplan-Meier analysis, which showed that prophylactic NUCs presented potential efficacy in improving PFS, however, without reaching statistical significance. (Figure 1C)

Differences in PFS between patients with or without HBV DNA negativity

Since the major effect of prophylactic NUCs was HBV DNA decreasing to undetectable level and the baseline HBV DNA between the two groups were not parallel, the HBV DNA negativity (HBV DNA at undetectable level at any time during this study for all the patients included) was used for further analysis. Similar patients in both group experienced HBV DNA negativity, which was 72 (64.3%) in the control group and 69 (75.8%) patients in the prophylactic group (p=0.076) (Table 1). Patients who experienced HBV DNA negativity presented significantly improved PFS compared with those whose HBV DNA tests were always positive. (Figure 1D)

Multivariate analysis for identifying independent prognostic factors for clinical outcomes of HCC patients receiving TACE

In order to determine prognostic factors of clinical parameters on the clinical outcome of HCC patients receiving TACE, multivariate analysis using a Cox proportional hazards model was used for independent significance by backward elimination. It revealed that usage of prophylactic NUCs and HBeAg positivity were the only significant variable associated with virologic events. And, prophylactic NUCs was the only significant predictor for hepatitis B flares (Table 2)

Furthermore, liver cirrhosis, more cycles of TACE and HBV DNA negativity presented protective factors for HCC patients receiving TACE regarding PFS. Moreover, higher CLIP score, lymph node metastasis, distant metastasis, breakout of hepatitis B flares and higher γ-glutamyl transpeptidase (GGT) were identified as independent risk factors for unfavorable PFS. (Table 2)

Lamivudine versus entecavir in HCC patients receiving TACE.

Patients using prophylactic lamivudine or entecavir were comparable in all the baseline characteristics. The

Table 3. Baseline Characteristics and Clinical Outcome of Patients in the Lamivudine Group and the Entecavir Group

Characteristics	Lamivudine group n=30	Entecavir Group n=46	*p*-value
Age (years, range)	51.7 (30.0-67.0)	51.0 (28.0-85.0)	0.865
Sex (n, %)			1.000
Male	28 (93.3%)	43 (93.5%)	
Female	2 (6.7%)	3 (6.5%)	
Liver cirrhosis (n, %)	23 (76.7%)	41 (89.1%)	0.256
ECOG Performance Status (n, %)			0.525
0-1	23 (76.7%)	38 (82.6%)	
2	7 (23.3%)	8 (17.4%)	
HBeAg (n, %)	7 (23.3%)	13 (28.3%)	0.633
Baseline HBV DNA (log10) (IU/ml)	4.80 (<2.0-6.82)	5.00 (<2.0-7.94)	0.387
Tumor number (n, %)			0.150
1	23 (76.7%)	42 (91.3%)	
>1	7 (23.3%)	4 (8.7%)	
CLIP- morphology (n, %)			0.508
0	17 (56.7%)	26 (56.5%)	
1	5 (16.7%)	4 (8.7%)	
2	8 (26.7%)	16 (34.8%)	
N stage (n, %)	1 (3.3%)	8 (17.4%)	0.136
M stage (n, %)	3 (10.0%)	3 (6.5%)	0.909
Portal invasion (n, %)	12 (40.0%)	19 (41.3%)	0.910
AFP (ng/ml) (n, %)			0.318
<400	21 (70.0%)	27 (58.7%)	
>400	9 (30.0%)	19 (41.3%)	
ALT (IU/l)	41 (23-121)	48 (10-135)	0.293
AST (IU/l)	46 (23-241)	58 (15-190)	0.271
Albumin (g/l)	37.4 (24.7-48.9)	37.3 (23.0-53.3)	0.953
GGT (IU/l)	93 (28-335)	114 (17-1136)	0.251
Alkaline phosphatase (IU/l)	102 (35-270)	104 (50-380)	0.807
Total bilirubin (mmol/L)	18 (4.7-109.8)	18.4 (5.2-84.4)	0.774
Fibrinogen (g/L)	3.00 (1.47-6.47)	2.95 (1.63-5.63)	0.807
INR median (median, range)	1.10 (0.77-2.21)	1.13 (0.88-1.66)	0.625
TACE cycles (median, range)	1 (1-6)	2 (1-6)	0.879
CLIP score (n, %)			0.115
0	5 (16.7%)	15 (32.6%)	
1	11 (36.7%)	6 (13.0%)	
2	6 (20.0%)	7 (15.2%)	
3	3 (10.0%)	7 (15.2%)	
4	5 (16.7%)	8 (17.4%)	
5	0 (0.0%)	3 (6.5%)	
Child-Pugh score (n, %)			0.950
A	21 (70.0%)	33 (71.7%)	
B	8 (26.7%)	12 (26.1%)	
C	1 (3.3%)	1 (2.2%)	
Clinical outcome			
Virologic Response (n, %)	20 (66.7%)	36 (78.3%)	0.262
Virologic Event (n, %)	4 (13.3%)	4 (8.7%)	0.794
Hepatitis B flares* (n, %)	1 (3.3%)	0 (0.0%)	0.828

* Hepatitis B flares due to HBV reactivation. Abbreviation: ECOG, Eastern Cooperative Oncology Group; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; CLIP, Cancer of the Liver Italian Program; AFP, a-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transpeptidase; INR, International normalized ratio; TACE, transcatheter arterial chemoembolization. P-values were calculated using the Mann-Whitney test, chi-square test or Fisher exact test if indicated

patients receiving prophylactic lamivudine presented similar virologic events (13.3% *vs* 8.7%, p=0.794) and hepatitis flares due to HBV reactivation (3.3% *vs* 0.0%, p=0.828) compared with patients using entecavir (Table 3, Figure 2A and Figure 2B). Furthermore, Kaplan-Meier analysis confirmed these results. Moreover, the influence on PFS of lamivudine and entecavir was comparable illustrated by Kaplan-Meier analysis (p=0.791) (Figure 2C).

Discussion

It is universally advised that patients with chronic HBV infection should receive prophylactic antiviral before commence of chemotherapy. The aim for prophylactic NUCs was set to be prevention of HBV reactivation (Li et al., 2012b; Liver, 2012; Yeo and Chan, 2013). Meanwhile, NUCs played specific roles for HCC patients. NUCs were used for prevention of tumor occurrence for

chronic HBV infected patients and for reducing tumor recurrence for HCC patients after radical surgery (Lok and McMahon, 2009). Regarding HCC patients receiving TACE, high incidence of HBV reactivation and its latent risk were reported previously and the preventive effects of prophylactic lamivudine were presented in a clinical trial (Jang et al., 2004; Jang et al., 2006; Lao et al., 2013). However, the efficacy of prophylactic NUCs on tumor control in these patients was still undetermined. In present study, prophylactic NUCs presented significant efficacy on prevention of HBV reactivation. However, its value on tumor control was not illustrated. Inconformity in baseline characteristics might be the cardinal causes. Since the major effect of prophylactic NUCs was decreasing HBV DNA to undetectable level (Liver, 2012), HBV DNA negativity was used to adjust the bias on the baseline characters. Survival analysis and multivariate analysis confirmed that patients presenting undetectable HBV DNA level displayed a significantly improved PFS. Similarly, previous report found that high pre-TACE serum level of HBV DNA was associated with poor overall survival (OS) and shortened time to progression (TTP) for HCC patients after TACE (Yu et al., 2013). Thus, it shall be reasonable to conclude that for HCC patients receiving TACE with positive HBV DNA level, effective prophylactic antiviral shall provide them prolonged PFS and improved prognosis.

The prognostic factors for HCC patients receiving TACE were far from identified (Li et al., 2012a). Previous studies indicated that tumor effect at 1 week after TACE (Bruix and Sherman, 2011), T stage (Eltawil et al., 2012), lactate dehydrogenase (Scartozzi et al., 2012), a-fetoprotein (Wang et al., 2012), pretreatment serum level of HBV DNA (Yu et al., 2013), C-reactive protein (Hongthanakorn et al., 2011) and blood neutrophil-to-lymphocyte ratio (Huang et al., 2011). However, few studies came to widely accepted results. The latent causes based on the nature of the TACE. The prognosis of HCC patients receiving local invasive therapy based on their fitness and tolerance to therapy. Refractoriness to TACE was the major causes for unfavorable OS, which was not easily to evaluate (Bruix and Sherman, 2011). Thus, prognostic analysis for HCC patients receiving TACE shall focus on the PFS, which indicated the need for further local regional therapy. In present study, we found that existence of tumor lesion-lymph node and distant metastasis-was a significant predictor for tumor progression. Besides, tumor initiating factors, high HBV DNA and hepatitis flares, was another prognostic factors for PFS. CLIP score, as the most accepted prognostic system for HCC patients worldwide (Li et al., 2013b), presented promising potential in the prognosis of HCC patients receiving TACE. Thus, persistent existence of tumor residual and tumor initiating factors might be the causes of tumor progression for HCC patients receiving TACE.

The present study firstly compared the efficacy of lamivudine and entecavir in HCC patients receiving TACE. Nowadays, clinical guidelines recommended entecavir as a preferable agent among all the prophylactic NUCs for its high antiviral potential and strong resistance barrier (Liver, 2012). However, the majority of evidence was based on the studies of prophylactic lamivudine, instead of entecavir (Nagamatsu et al., 2004; Jang et al., 2006). In present study, we found that lamivudine presented similar effect with entecavir. Early virologic events were found in patients receiving prophylactic entecavir, whose causes might not be virus breakthrough but rather poor compliance of patients (Hongthanakorn et al., 2011). Late virologic events in lamivudine group shall be identified as virus breakthrough. Based on our results, we recommended that patient education was imperative for the success of prophylactic NUCs. And, entecavir was a preferable agent for HCC patients regarding virus resistance.

The endpoint of antiviral prophylaxis should be designed based on the nature history of HBV reactivation (Li et al., 2012b). HBV reactivation consisted of at least two stages: increase of viral replication and hepatitis flares. 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, prophylactic NUCs presented a nearly 85% reduction of virological events, which finally leaded to a deceased incidence of hepatitis flares. Thus, virologic events might be a more preferable endpoint for future studies regarding HBV reactivation.

Then, we found that liver cirrhosis was a protective factor for PFS without identifying the mechanism. Patients with liver cirrhosis might receive more intensive evaluation, which lead to early detection of tumor. The efficacy of adefovir was not analyzed in our study due to limited sample size, which was the weakness of our study.

In summary, this study identified the efficacy of prophylactic NUCs on prevention of HBV reactivation in HCC patients receiving TACE. Well managed administration of entecavir was a preferable prophylaxis. Achievement of undetectable HBV DNA level displayed a significant capability in improving PFS. Besides, persistent existence of tumor residual lesion, positive HBV DNA and hepatitis B flares might be the causes of tumor progression for these patients.

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