

Nucleos(t)ide analogs in the prevention of hepatitis B virus related hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is among the most common cancer types and causes of cancer related mortality worldwide. Almost 50% of all HCC cases globally are attributable to chronic hepatitis B virus (HBV) infection. The incidence rates of HCC in untreated Asian subjects with HBV infection was estimated to be 0.2% in inactive carriers, 0.6% for those with chronic hepatitis without cirrhosis, and 3.7% for those with compensated cirrhosis. In Western populations, HCC incidences are

reported to be 0.02% in inactive carriers, 0.3% in subjects with chronic hepatitis without cirrhosis, and 2.2% in subjects with compensated cirrhosis. Despite effective antiviral treatment options which are able to transform chronic hepatitis into an inactive carrier state, the risk of HCC cannot be fully ruled out to exclude those patients from surveillance. Newer nucleos(t)ide analogues (NAs) as entecavir and tenofovir are very potent in terms of sustained virological suppression which leads to improved liver histology. However, they do not have any influence on the cccDNA or integrated DNA of HBV in the liver. Nonetheless, viral replication is the only modifiable component among the established risk factors for HBV-related HCC with the current treatment options. In this review, it was aimed to summarize cumulative evidence behind the concept of prevention of HBV related HCC by NAs, and to discuss remaining obstacles to eliminate the risk of HCC.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Prevention; Nucleos(t)ide analogues; Risk factors

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Core tip: After the introduction of potent nucleos(t)ide analogues with high genetic barrier to resistance, maintaining long-term virological suppression is achievable in almost all patients with chronic hepatitis B. The currently recommended first-line antiviral drugs, entecavir and tenofovir, can significantly reduce hepatocellular carcinoma (HCC) incidence, but the observed risk under efficient therapy is not zero in the long-term. There are established risk factors including age, gender, family history, low platelet levels, presence of cirrhosis or severity of liver disease, which should be incorporated into the clinical decision making to differentiate those patients under risk of developing HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and third most common cause of cancer related mortality worldwide^[1]. HCC virtually always develops within a background chronic liver disease. Globally, almost 50% of all HCC cases are attributable to chronic hepatitis B virus (HBV) infection^[2]. HCC incidence is highly variable in different geographic locations and the distribution of the disease may be different even among ethnic groups living in the same country^[1]. These differences are most probably due to geographical variations in the prevalence of hepatitis viruses. In Sub-Saharan Africa and Asia most cases of HCC develop in the presence of chronic hepatitis B (CHB) infection (up to 60%), however in Western countries only up to 20% of cases can be attributed to HBV infection^[2]. Fortunately, after the introduction of universal vaccination programs throughout the world, the incidence of CHB infection was significantly decreased^[3]. In the countries that have adopted the HBV vaccination program, a significant decrease in carrier rates as well as complications including HCC development have been experienced^[4]. However, HBV infection is still a major health problem in most parts of the world and development of HCC is an important complication of chronic infection, even in inactive carrier patients^[5]. In cirrhotic patients, surveillance for HCC increases the possibility of an earlier diagnosis that gives the patient a chance to undergo curative treatments^[2]. However, current recommendations for screening of HCC in patients at risk is far from being satisfactory, and prognosis remains poor because treatment options are rather non-curative in advanced stages of the disease^[6]. In this context, it is imperative to implement preventive strategies in patients with CHB infection. Despite effective antiviral treatment options which are able to transform chronic hepatitis into an inactive carrier state, the risk of HCC cannot be fully ruled out to exclude those patients from surveillance.

LITERATURE STUDY

In this review, it is sought to summarize the cumulative evidence on the role of antiviral therapy with NAs in the chemoprevention of HCC. Studies on prevention of HBV-related HCC were identified through electronic and manual search using online databases including MEDLINE and Web of Science. The relevant papers and conference proceedings in English language published from January, 2001 to January, 2015 were searched using following keywords: HCC, HBV, prevention, recurrence, curative treatment, resection, nucleos(t)ide analogue (NA), lamivudine, adefovir, telbivudine, entecavir, tenofovir. Selected studies were grouped

according to one of the following topics: (1) NAs in chemoprevention of HCC; (2) HCC risk in patients who clear hepatitis B surface antigen (HBsAg); and (3) HCC recurrence risk in patients with HBV-related HCC after curative treatments. Both randomized-controlled and non-randomized studies were considered for inclusion. Uncontrolled studies were excluded unless an estimated HCC risk model was used to assess efficacy of NAs on HCC incidence. Reference lists of all papers, including reviews and meta-analyses, found during electronic search were checked manually to find relevant articles. The papers which were judged to be pertinent to the topic exceeded 100, and the number of included full-length articles were 51.

HBV AND THE RISK OF HCC

The association between HBV infection and development of HCC is well-established and has been demonstrated in several studies. In an early prospective controlled study from Asia, it was shown that the annual incidence of HCC was 0.5% in HBV-infected individuals; and the risk increased with age where annual incidence reached 1% at the age of 70^[7]. HBV-infected subjects were found to be 100 times more likely to develop HCC compared to uninfected subjects. The incidence ratio for HCC was even higher as much as 2.5% per year in patients with known cirrhosis. In a recent study by Chen *et al*^[5], a lesser but still substantial risk of HCC development was reported in an Asian cohort of patients with inactive HBV infection. In this study, the authors reported an annual incidence rate of 0.06% for HCC development with a relative risk of 4.4 compared to uninfected controls. In Western populations most studies are inadequate to draw conclusions and results are variable. This discrepancy between incidence rates among studies is probably due to the different patient settings (referral or population-based) and definitions for the HBV carrier state. Annual rates as high as 0.47% was reported in a study by Sherman *et al*^[8], which can be explained by high prevalence (71%) of Asian background in this North American population. Yet, most studies reported that annual incidence of HBV-related HCC in Europe or North America seems to be less significant^[9,10], and it is generally accepted to be around or less than 0.2%^[11]. Therefore, it is not clear if surveillance is worthwhile or when is it cost-effective to start screening in Caucasian populations. HBV-infected patients with African ancestry seem to possess a higher risk of developing HCC, particularly at a younger age^[12]. A database analysis from the United States reported higher incidence rates among Asians/Pacific Islanders, blacks, Native Americans/Alaska Natives, compared to people with European ancestry^[13]. Although HCC may arise in the setting of inactive HBV infection, most patients with HBV who develop HCC have cirrhosis either long-standing or undiagnosed at the time of HCC diagnosis^[14,15]. In a review of cohort studies^[16], it was summarized that incidence rates of HCC in

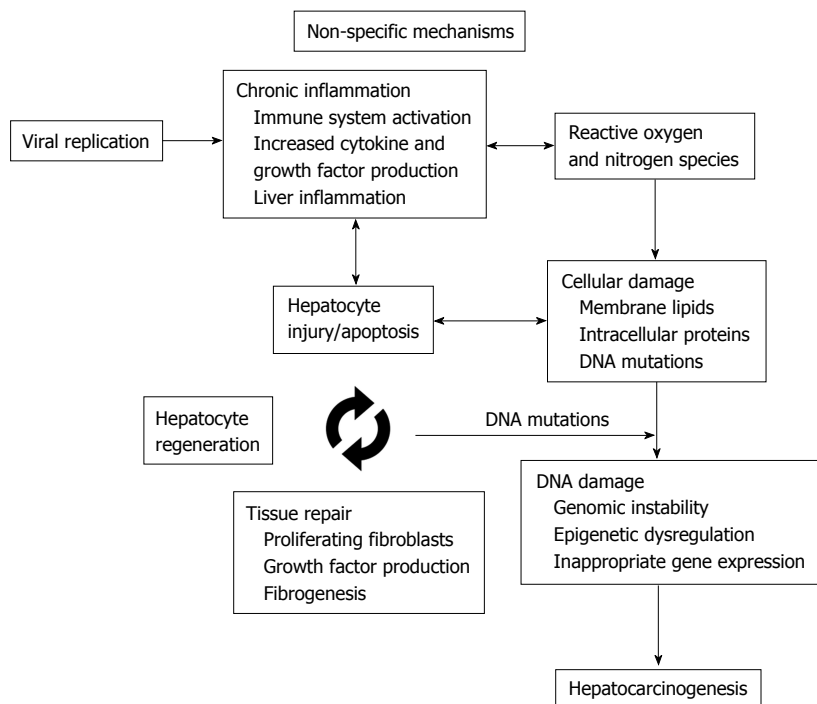


Figure 1 Chronic inflammation in the liver is characterized by sustained damage leading to hepatocyte death/regeneration and tissue repair cycle. Activation of inflammatory signaling with increased cytokine and growth factor production leads to oxidative stress which contributes to cellular damage. Cumulative damage to cellular structures, proteins and chromosomes alters genomic and epigenomic functions which can eventually induce hepatocarcinogenesis.

Asian subjects with HBV infection was estimated to be 0.2% in inactive carriers, 0.6% for those with chronic hepatitis without cirrhosis, and 3.7% for those with compensated cirrhosis. With an attention to inadequacy of studies in Western populations, they calculated an annual incidence rate of 0.02% in inactive carriers, 0.3% in subjects with chronic hepatitis without cirrhosis, and 2.2% in subjects with compensated cirrhosis.

There are a number of factors other than cirrhosis and ethnicity that have been reported to increase HCC risk among HBV carriers. Patient related factors include male gender, older age, high alcohol consumption and family history of HCC, and viral factors include duration of infection, higher viral replication, HBV genotype, and co-infection [hepatitis C, hepatitis D or human immunodeficiency virus (HIV)]^[14]. Recently, it was also shown that high levels of HBsAg titer (HBsAg \geq 1000 IU/mL) is associated with increased risk of HCC in CHB patients with low viral load (HBVDNA < 2000 IU/mL)^[17].

MECHANISMS OF HBV-ASSOCIATED HEPATOCARCINOGENESIS

An interaction of complex mechanisms and pathways contribute to the initiation of hepatocarcinogenesis. HBV infection is among the most important risk factors for development of HCC, and can influence carcinogenesis by multiple ways. Chronic inflammation, a driving factor in many types of cancers, is an important pathogenetic mechanism for development of HBV-related HCC. Chronic inflammation in the liver is characterized by sustained

hepatic damage, damage-induced apoptosis, hepatocyte death/regeneration cycle, and tissue repair. In addition to continuous cycle of cell death and regeneration, constant activation of inflammatory signaling and increased cytokine production by innate and adaptive immune system contribute to generation of reactive oxygen and nitrogen species which can cause damage to important cellular components including cytoplasmic membrane lipids, intracellular proteins and DNA^[18,19]. Genomic instability and alterations in epigenetic regulation of genes can cause inappropriate gene expression and enhanced proliferation of induced cells leading to neoplastic changes in susceptible individuals (Figure 1)^[20]. Interestingly, induced cells may have clonal properties which were demonstrated in experimental models that show clonal hepatocyte repopulation is a major risk factor for HCC development^[21,22]. In addition to non-specific hepatocarcinogenesis by chronic inflammation, HBV has unique virus-specific mechanisms involving the viral proteins HBx and preS/S, and the insertional mutagenesis with integration of HBV-DNA into the host genome that alters the expression of endogenous genes or induces chromosomal instability, and causes epigenetic changes including alterations in genomic methylation and regulation of microRNA expression (Figure 2)^[23].

NAs IN CHEMOPREVENTION OF HCC

The real key for certain prevention of HBV-related HCC is vaccination against the virus for newborns and people at risk. However in the absence of definitive curative treatment, there is a need for accurate risk estimation

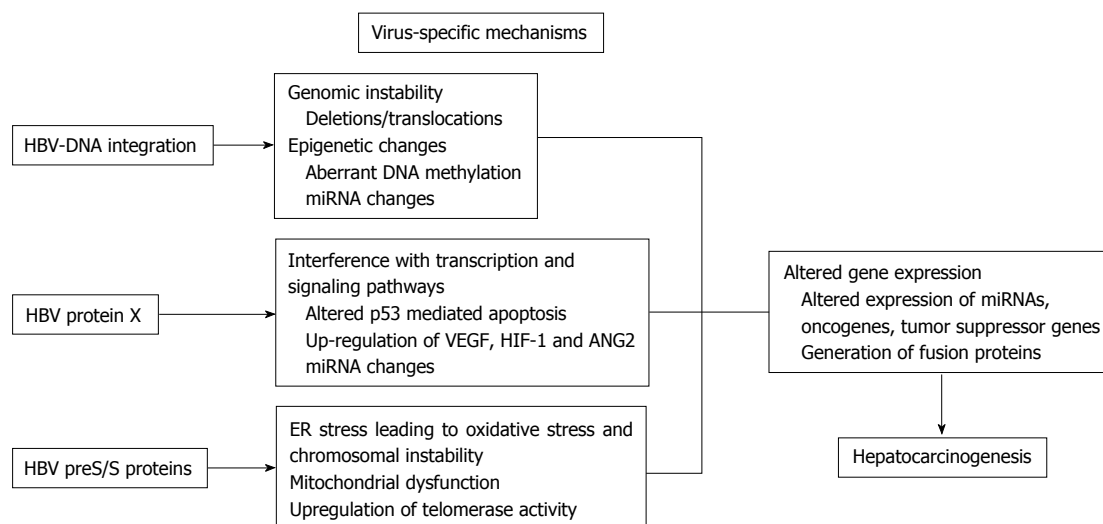


Figure 2 Hepatitis B virus has unique virus-specific mechanisms to induce carcinogenesis in the liver. The integration of hepatitis B virus (HBV)-DNA into the host genome alters DNA expression by gene and/or chromosomal deletions/translocations, and epigenetic changes (aberrant DNA methylation, miRNA changes). Viral protein HBV protein X may cause interference with transcription and signaling pathways leading to altered p53 mediated apoptosis and angiogenesis by up-regulation of vascular endothelial growth factor (VEGF), hypoxia inducible factor-1 (HIF-1) and angiopoietin-2 (ANG2). HBV preS/S proteins cause endoplasmic reticulum stress and mitochondrial dysfunction leading to oxidative stress.

and modification in patients with chronic infection. Among the established risk factors for HBV-related HCC, patient or virus-related factors cannot be modified except viral replication. In a large prospective cohort by REVEAL-HBV study group, the relationship between HBV-DNA titer and HCC risk was demonstrated without any doubt^[24,25]. Currently, there are five NAs approved for the treatment of patient with CHB: lamivudine, telbivudine, adefovir, entecavir and tenofovir disoproxil^[26]. In the era of antiviral drugs with high barrier to resistance, we can suppress HBV-DNA in almost all patients receiving NAs, but the question remains if treatment prevents the development of HCC in every patient.

Lamivudine is a potent reverse transcriptase inhibitor which was originally developed for the treatment of patients with HIV infection. It is the first oral antiviral drug that was approved for treatment of patients with CHB. Lamivudine monotherapy in patients with CHB is associated with ALT normalization, HBV-DNA suppression, hepatitis B "e" antigen (HBeAg) sero-conversion^[27,28], and histological improvement (regression of necroinflammation and fibrosis) in the long-term^[29]. The role of NAs to prevent HCC has been thoroughly investigated in multiple studies but the largest number of studies available considered only lamivudine. The studies which investigated effects of NAs in reduction of HCC risk in CHB are summarized in Table 1. In a study by Liaw *et al*^[30], which evaluated long-term benefits of lamivudine monotherapy included 651 CHB patients with biopsy-proven advanced fibrosis or cirrhosis in a prospective randomized-placebo controlled setting. This pivotal study was terminated early due to significant beneficial effects seen in the treatment arm. Specifically, HCC development was observed in 3.9% of the patients in the treatment group and 7.4% of those in the placebo group with a hazard ratio of 0.49 ($P = 0.047$). In the

same year, AISF (Italian Association for the Study of Liver Disease) Lamivudine Study Group investigated the effect of lamivudine treatment on the outcome of patients with HBeAg-negative CHB in a multicenter retrospective study^[31]. They found that cirrhotic patients with maintained virological response were less likely to develop HCC and disease worsening. But, presence of cirrhosis and virological breakthrough were independently related to mortality and development of HCC. In another randomized-controlled trial by Chan *et al*^[32], HBeAg-negative CHB patients were enrolled to lamivudine (100 mg/d) or placebo arms to investigate the efficacy of 2-year lamivudine treatment. Apparently, they did not find a risk reduction for HCC, but the study was not designed to answer this question and sample size was too small to get conclusions. Owing to undeniable beneficial effects of lamivudine therapy in CHB, subsequent randomized-controlled studies cannot be conducted to evaluate the influence of NAs. Thereafter, multiple case-control studies and prospective or retrospective cohort studies using historical controls were published. In a retrospective cohort study in Japan by Matsumoto *et al*^[33], which included 377 treated patients (lamivudine 100 mg/d) vs 377 matched untreated controls showed a significant risk reduction for HCC in treated cohort (0.4% per year vs 2.5% per year, $P < 0.001$). Several other Asian cohort studies from China^[34,35], South Korea^[36-38] and India^[39] also confirmed the protective effect of antiviral therapy with lamivudine against development of HCC. The evidence behind HCC chemoprevention with oral antivirals comes largely from Asian cohort studies; however data obtained in Caucasian populations also exists. In a European cohort study from Greece, Papatheodoridis *et al*^[40] reported that lamivudine (with adefovir switch or add-on therapy when required) treatment significantly improved survival

Table 1 Summary of controlled studies investigating the effect of nucleos(t)ide analogues on hepatocellular carcinoma risk among treated and untreated patients with chronic hepatitis B

Ref.	Country/region	Study type	Treatment	No. of patients (T/C)	Patient cohort	Follow-up (T/C), mean or median (yr)	Treatment outcome
Liaw <i>et al</i> ^[30]	Asia	RCT	Lamivudine (100 mg/d)	436/215	Advanced fibrosis or cirrhosis	2.7/2.7	Reduced HCC risk
Manolakopoulos <i>et al</i> ^[80]	Greece	Case-control	Lamivudine (100 mg/d)	30/30	Decompensated cirrhosis	1.5/1.8	No risk reduction
Matsumoto <i>et al</i> ^[33]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	377/377	Chronic hepatitis B (any stage)	2.7/5.3	Reduced HCC risk
Papatheodoridis <i>et al</i> ^[40]	Greece	Retrospective cohort	Lamivudine (adefovir switch or add-on when required)	201/195	HBeAg-negative chronic hepatitis B	3.8/6.1	Better overall survival. Reduced risk of major events including HCC
Chan <i>et al</i> ^[32]	China	RCT	Lamivudine (100 mg/d)	89/47	HBeAg-negative chronic hepatitis B	2.5/2.5	No risk reduction
Yuen <i>et al</i> ^[34]	China	Prospective cohort	Lamivudine (25-100 mg/d)	142/124	HBeAg-positive chronic hepatitis B	7.5/9.0	Reduced cirrhosis/HCC risk
Lee <i>et al</i> ^[36]	South Korea	Retrospective cohort	Lamivudine (100 mg/d)	589/589	Chronic hepatitis B (any stage)	2.9/5.3	Reduced HCC risk
Ma <i>et al</i> ^[35]	China	Prospective cohort	Lamivudine (100 mg/d)	41/176	Cirrhosis	3.16/NS	Reduced HCC risk
Das <i>et al</i> ^[39]	India	Case-control	Lamivudine or adefovir	151/102	Decompensated cirrhosis	4.0/3.8	Less HCC rate in treated group
Eun <i>et al</i> ^[37]	South Korea	Retrospective cohort	Lamivudine (100 mg/d)	872/699	Chronic hepatitis B (any stage)	4.7/5.7	Reduced HCC risk in cirrhotic patients with SVS
Kim <i>et al</i> ^[38]	South Korea	Retrospective cohort	Lamivudine and/or adefovir, or entecavir	240/481	Cirrhosis	3.9/4.3	Better overall survival. Reduced HCC risk (borderline significance)
Hosaka <i>et al</i> ^[46]	Japan	Retrospective cohort	Entecavir (0.5 mg/d)	316/316	Chronic hepatitis B (any stage)	3.3/7.6	Reduced HCC risk
Wong <i>et al</i> ^[47]	China	Retrospective cohort	Entecavir (0.5 mg/d)	1446/424	Chronic hepatitis B (any stage)	3.0/9.5	Reduced HCC risk in cirrhotic patients
Kumada <i>et al</i> ^[81]	Japan	Retrospective cohort	Lamivudine ± adefovir, entecavir	117/117	Chronic hepatitis B (any stage)	12.3/11.6	Reduced HCC risk
Sievert <i>et al</i> ^[49]	Reg. trial (abstract)	Prospective cohort	Tenofovir (300 mg/d)	641	Chronic hepatitis B (any stage)	6	Reduced HCC risk compared to estimated risk (REACH-B model)
Su <i>et al</i> ^[48]	Taiwan	Prospective cohort	Entecavir (0.5 mg/d)	1123/503	Cirrhosis (HBVDNA > 2000 IU/mL)	3.6/6.8	
Wu <i>et al</i> ^[44]	Taiwan	Retrospective nationwide cohort	Lamivudine, adefovir or entecavir	21595/21595	Chronic hepatitis B (any stage)	3.5/5.2	Reduced HCC risk
Gordon <i>et al</i> ^[82]	United States	Retrospective cohort	94% received NAs, remaining received IFNs	820/1851	Chronic hepatitis B (any stage)	5.2	Reduced HCC risk
Coffin <i>et al</i> ^[83]	United States	Retrospective cohort	NAs	322	Chronic hepatitis B (any stage)	3.2	Reduced HCC risk compared to estimated risk (REACH-B model)

NAs: Nucleos(t)ide analogues; HCC: Hepatocellular carcinoma; T: Treatment group; C: Control group; RCT: Randomized-controlled trial; HBeAg: Hepatitis B e antigen; SVS: Sustained virological suppression; IFNs: Interferons.

and reduced the risk of major events including HCC compared to interferon non-sustained responders and untreated controls.

Despite these encouraging results of lamivudine monotherapy, the development of resistant strains of HBV have been the main problem since it was introduced into the clinical practice. An important finding of the study by Liaw *et al*^[30] was that clinical deterioration defined as ≥ 2 increase in Child-Pugh score was significantly more frequent in patients who develop YMDD mutation under lamivudine treatment. In a large cohort study from South

Korea, lamivudine treatment reduced the incidence of HCC both in patients with CHB and cirrhosis, yet the risk reduction was significant only for compensated cirrhotic patients and when the viral suppression was sustained^[37]. Patients with virological breakthrough or suboptimal response during lamivudine therapy were shown to have an increased risk for HCC which was comparable to untreated controls. Kurokawa *et al*^[41] evaluated 283 patients with CHB treated with lamivudine 100 mg/d in an uncontrolled cohort study. They found that maintained virological response, presence of cirrhosis, and age are

independent risk factors for development of HCC in patients under lamivudine therapy.

In the era of NAs with high genetic barrier against resistance, entecavir and tenofovir are the only oral antiviral drugs recommended by major society treatment guidelines for CHB^[26,42,43]. However, the evidence behind these novel oral antivirals regarding HCC risk reduction is scarce. In the largest retrospective nationwide CHB cohort from Taiwan^[44], the investigators included 21595 matched patients in the treatment and control groups. Most of the patients were treated by lamivudine, yet 5748 patients received entecavir 0.5 mg/d. The treated cohort had a significantly lower 7-year incidence of HCC (7.32%; 95%CI: 6.77%-7.87%) than controls (22.7%; 95%CI: 22.1%-23.3%; $P < 0.001$). After adjusting for confounding factors, NA treatment was associated with a reduced risk of HCC, with an adjusted hazard ratio of 0.37 (95%CI: 0.34-0.39; $P < 0.001$). However, the authors did not report if there were any differences between lamivudine and entecavir treated patients regarding HCC incidence. In a randomized trial of 191 patients with decompensated cirrhosis, entecavir-treated patients tended to have a lower incidence of HCC than those treated with adefovir, but the risk reduction was not statistically significant (HR = 0.74, 95%CI: 0.46-1.18, $P = 0.20$)^[45]. A recent study from Japan that compared the incidence of HCC in entecavir-treated patients and a matched historical cohort of untreated patients (316 vs 316 patients), the investigators found a significantly reduced risk of HCC in the treated group (5 years incidence rates were 3.7% and 13.7% for the treatment and control groups, respectively; $P < 0.001$)^[46]. They also compared treatment effect between matched entecavir and lamivudine-treated patients without rescue therapy. It was reported that when the control group was taken as reference HCC risk reduction was more profound in entecavir-treated cirrhotic patients than it is for lamivudine-treated cirrhotic patients ($P < 0.001$ vs $P = 0.019$). Of note, this effect was seen in cirrhotic patients but not in non-cirrhotics. In a study from China by Wong *et al*^[47], the cumulative probability of HCC between entecavir and untreated historical controls were comparable ($P = 0.82$). However, entecavir-treated patients with radiological cirrhosis had a significantly lower 5-year cumulative probability of HCC (13.8% vs 26.4%, $P = 0.036$) compared to the untreated patients with cirrhosis. This effect was more profound in cirrhotic patients with maintained virological suppression. On the other hand, entecavir-treated patients with cirrhosis who failed to achieve undetectable HBV-DNA had a comparable risk of HCC with the untreated patients. In a recent multicenter study from Taiwan^[48], 1123 patients with HBV-related cirrhosis treated with entecavir were compared to 503 historical controls with HBV-related cirrhosis. All patients had baseline serum HBV-DNA level > 2000 IU/mL. Although treated patients were significantly older and had more advanced liver disease compared to historical controls, entecavir treatment was shown to be associated with an adjusted hazard

ratio of 0.40 (95%CI: 0.27-0.60) in cirrhotic patients. After adjusting for age, the multivariate analysis showed that male gender, no treatment, lower albumin level and lower platelet count were independent risk factors associated with HCC development.

There are very few data regarding treatment effect of tenofovir on HCC incidence. One of them comes from post-hoc analysis of the registration trial of tenofovir, which was reported as an abstract. In this report by Sievert *et al*^[49], investigators included 641 patients with CHB receiving open-label tenofovir therapy for 6 years and compared HCC incidence with the estimated risk calculated by REACH-B model^[50]. They reported that 14 tenofovir-treated patients (6 of them were cirrhotic) developed HCC during the follow-up and the incidence of HCC decreased with a standardized incidence ratio of 0.45 (95%CI: 0.23-0.91) compared to the estimated risk. Despite the low number of HCC cases in this study, they concluded by emphasizing continued surveillance for CHB patients receiving long term oral antiviral treatment.

There are several meta-analyses or systematic reviews that confirmed the beneficial effects of NAs in the prevention of HCC in CHB. In a systematic review by Papatheodoridis *et al*^[51], 21 studies were reviewed and 3 of them which were of high quality and included untreated controls. In the pooled analysis of 3 studies, HCC was detected significantly less frequently in treated than in untreated patients (2.8% vs 6.4%, respectively, $P = 0.003$). Interestingly, they found that incidence of HCC was significantly higher in untreated patients even when compared to treated patients with virological breakthroughs or no response. Similarly, other meta-analyses confirmed these results regarding the influence of NAs on HCC risk (Table 2)^[52-54].

Although it is evident to say that antiviral therapy decrease HBV-related HCC incidence when compared with the natural course of the disease, there are sufficient data showing that antiviral therapy does not eliminate the HCC risk completely, even in non-cirrhotic patients with sustained virological suppression. Papatheodoridis *et al*^[55] included 818 patients with HBeAg-negative CHB treated with NAs in a retrospective study investigating HCC incidence. All patients were treated with NAs starting with lamivudine monotherapy, and during a median follow-up of 4.7 years 49 patients (6%) eventually developed HCC. The study demonstrated a trend for lower cumulative HCC incidence in CHB patients with virological on-therapy remission ($P = 0.076$), which was defined as maintained undetectable HBV-DNA (< 200 IU/mL). However, virological remission did not significantly influence the incidence of HCC in patients with cirrhosis (0.327). Moreover, multivariate analysis revealed that age, gender and cirrhosis were independently associated with HCC risk regardless of virological remission. In a recent study by Arends *et al*^[56], 14 of 744 patients (42% Caucasian ethnicity) with CHB developed HCC during a median follow-up of 167 wk. Nine (64%) patients among them had

Table 2 Systematic review and meta-analyses investigating hepatocellular carcinoma risk reduction in patients receiving nucleos(t)ide analogues vs untreated controls

Ref.	No. of studies	No. of patients (T/C)	OR (95%CI)	P
Papatheodoridis <i>et al</i> ^[51]	3	1313 (779/534)	0.43 (0.25-0.74)	0.002
Zhang <i>et al</i> ^[52]	6	3644 (2035/1609)	0.26 (0.15-0.47)	< 0.00001
Singal <i>et al</i> ^[53]	6	6877 (3306/3571)	0.48 (0.38-0.61)	< 0.00001
Sung <i>et al</i> ^[54]	5	2289 (1267/1022)	0.22 (0.10-0.50)	0.0003

T: Treatment group; C: Control group.

cirrhosis at baseline, and 12 patients developed HCC even after achieving virological response (HBV-DNA < 80 IU/mL). The 5-year cumulative incidence rate of HCC was reported to be low for non-cirrhotic patients, yet it was significantly higher for cirrhotic patients (2.1% vs 10.9%, respectively, $P < 0.001$).

Several studies investigated independent risk factors associated with HCC development in patients receiving NAs. The factors commonly attributed to HCC risk in patients receiving NAs were age, male gender, duration of disease, presence of cirrhosis and no virological response^[41,51,55,57-59]. Recently in a large European retrospective multicenter cohort of 1666 patients with CHB (all Caucasian) treated with entecavir or tenofovir, 71 patients (4.3%) developed HCC within a median follow-up duration of 39 mo (range, 8-140 mo)^[60]. The importance of this study is that there was little information available regarding the risk factors of HCC in Caucasian patients treated with novel antiviral drugs. The authors reported an annual incidence rate of 1.37 (95%CI: 1.09-1.73) per 100 patient. The cumulative probability of developing HCC reached 8.7% after 5 years of antiviral therapy. In multivariate Cox regression analysis they found age, male gender, low platelet levels (< 100000/mm³), and liver disease severity were independently associated with subsequent development of HCC. Of note, they did not find a significant association between virological remission under treatment and risk of HCC development, which was contrary to previous studies. However, this result is probably related to the high virological remission rate (92%) under antiviral treatment. A recent study from Turkey; which investigated the risk of HCC development in 641 CHB patients on-therapy; showed that cirrhosis, NAs with low-genetic barrier against resistance, and development of resistance or virological breakthrough were independent predictors of HCC development^[61].

HCC RISK IN PATIENTS WHO CLEAR HBSAG

Whether it is spontaneous or therapy-induced, HBsAg clearance with or without anti-HBs seroconversion is considered highly beneficial. Although HBsAg loss or seroconversion has been the ultimate goal in the treatment of CHB, it is rarely achievable with the available NA options which have no influence on intra-

hepatic cccDNA of HBV. Nonetheless, it is still the holy grail of a treatment course which can be achieved by only a small group of patients, even in the long-term. However, until recently data was insufficient to determine if it is reasonable to exclude those patients who achieve HBsAg loss or seroconversion from routine clinical follow-up. Although there is evidence showing that disease progression may still occur after HBsAg loss^[62], the common practice have been continuing follow-up and HCC screening only in those with cirrhosis. This seems to be an evidence-based approach, because cirrhosis is the major risk factor for HCC and should be considered a premalignant condition even after HBsAg loss or seroconversion^[63]. In a recent study by Simonetti *et al*^[64], 1271 Alaskan native patients with CHB were included in a prospective population-based cohort study, and 158 patients achieved HBsAg loss during a mean follow-up duration of 19.6 years. The authors reported that 6 patients (2 of them were cirrhotic) developed HCC during a mean follow-up of 7.3 years after HBsAg clearance. Although the HCC incidence after HBsAg clearance was reported to be significantly lower than the rate in those who remained seropositive, the risk was still high enough to justify continuum of periodic follow-up visits with HCC surveillance.

HCC RECURRENCE RISK IN PATIENTS WITH HBV-RELATED HCC AFTER CURATIVE TREATMENTS

Despite advances in surgical techniques, survival after curative resection for HBV-related HCC remains dissatisfactory with recurrence rates of more than 50%^[65]. There is no proven adjuvant chemotherapeutic regimen that can reduce recurrence risk or improve patient survival after curative resection. However, the above mentioned body of data provides solid evidence that antiviral therapy in patients with CHB or cirrhosis reduces the risk of HCC development, leading to the notion that antiviral therapy might prevent recurrence and improve survival after curative therapy. There is convincing evidence that persistent high viremia is associated with increased risk of HCC recurrence in CHB patients who underwent resection for HBV-related HCC^[66,67]. Therefore, the aim has been focused on suppression of persistent HBV replication, which

Table 3 Summary of controlled studies investigating the efficacy of nucleos(t)ide analogues in prevention of hepatocellular carcinoma recurrence after curative treatments

Ref.	Country	Study type	Antiviral treatment	No. of patients (T/C)	HCC treatment	Follow-up (T/C), mean/median (yr)	Treatment outcome
Piao <i>et al</i> ^[69]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	30/40	Resection or ablation/TACE	Not specified	No risk reduction for HCC recurrence Better overall survival
Shuqun <i>et al</i> ^[70]	China	Retrospective cohort	Lamivudine (100 mg/d) + thymosin α 1	17/16	Resection	1-3	Reduced HCC recurrence (NS)
Kuzuya <i>et al</i> ^[71]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	16/33	Resection or RFA	3.2/2.7	No risk reduction
Kubo <i>et al</i> ^[72]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	14/10	Resection	2.1	Higher tumor-free survival
Yoshida <i>et al</i> ^[84]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	33/71	RFA	2.8/3.9	No risk reduction
Hung <i>et al</i> ^[85]	China	Retrospective cohort	Lamivudine (100 mg/d)	10/62	Resection	1.6	Reduced HCC recurrence
Koda <i>et al</i> ^[86]	Japan	Retrospective cohort	Lamivudine or entecavir	30/20	Resection or ablation/TAE	2.4/3.0	No risk reduction for HCC recurrence Better overall survival
Chuma <i>et al</i> ^[87]	Japan	Retrospective cohort	Lamivudine (100 mg/d)	39/64	Resection or RFA	2.9/4.4	Reduced HCC recurrence
Li <i>et al</i> ^[74]	China	Prospective cohort	Lamivudine \pm adefovir	43/36	Resection	1.0	No risk reduction
Chan <i>et al</i> ^[73]	China	Retrospective cohort	Lamivudine or entecavir	42/94	Resection	Not specified	Reduced HCC recurrence
Urata <i>et al</i> ^[88]	Japan	Retrospective cohort	Not specified	46/24 ²	Resection	3.1	Tumor-free survival is better vs patients with high viral load
Yang <i>et al</i> ^[89]	China	Prospective cohort	Lamivudine, adefovir or entecavir	142/188	Resection	4.0	Reduced HCC recurrence
Wu <i>et al</i> ^[75]	Taiwan	Retrospective nationwide cohort	Nucleoside analogue(s)	518/4051	Resection	2.6/2.2	Reduced HCC recurrence
Huang <i>et al</i> ^[90]	China	Prospective cohort	Lamivudine, adefovir or entecavir	865/175	Resection (HBVDNA > 2000 IU/mL)	3.5	Better disease-free survival (borderline significance) Better overall survival
Huang <i>et al</i> ^[68]	China	Retrospective cohort	Lamivudine, adefovir or entecavir	150/1459	Resection (HBVDNA < 2000 IU/mL)	2.9-3.3	Better disease-free survival
Ke <i>et al</i> ^[91]	China	Retrospective cohort	Lamivudine (100 mg/d)	141/337	Resection	2.0/1.9	No risk reduction for HCC recurrence Better overall survival
Su <i>et al</i> ^[92]	Taiwan	Retrospective cohort	Lamivudine, entecavir or pegylated interferon	62/271	Resection	3.8	Reduced HCC recurrence Better overall survival
Yin <i>et al</i> ^[76]	China	2 cohorts (RCT and NRC)	Lamivudine ¹ (100 mg/d)	RCT: 81/82; NRC: 215/402	Resection	RCT: 3.3; NRC: 1.98	Reduced HCC recurrence and better overall survival in both cohorts
Yeh <i>et al</i> ^[93]	Taiwan	Retrospective cohort	Entecavir, lamivudine, telbivudine, or combination	490/3369	Resection, RFA, PEI	3.3/3.3	No benefits for HCC progression or overall survival
Zhang <i>et al</i> ^[94]	China	Retrospective cohort	Entecavir (0.5 mg/d)	40/47	Resection	2.6	Reduced recurrence if HCC \leq 3 cm
Hann <i>et al</i> ^[95]	United States	Retrospective cohort	NAs	16/9	Resection, RFA, PEI, TACE	5.0	Reduced HCC recurrence Better overall survival
Nishikawa <i>et al</i> ^[96]	Japan	Retrospective cohort	Lamivudine, adefovir or entecavir	99/32	Resection, RFA, PEI	3.5/4.0	No risk reduction for HCC recurrence Better overall survival
Huang <i>et al</i> ^[77]	China	RCT	Adefovir (10 mg/d) Switch to entecavir (18 patients)	100/100	Resection	5.0	Reduced HCC recurrence Better overall survival
Chong <i>et al</i> ^[97]	China	Retrospective-prospective cohort	Nucleoside analog(s)	254/150	Resection	3.3/3.6	No risk reduction for HCC recurrence Better overall survival

¹Adefovir \pm lamivudine or entecavir for drug resistance; ²13 patients with high viral load, 11 patients with low viral load. HCC: Hepatocellular carcinoma; T: Treatment group; C: Control group; NS: Not significant; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; NAs: Nucleos(t)ide analogues; RCT: Randomized-controlled trial; NRC: Non-randomized cohort.

Table 4 Summary of meta-analyses which investigated preventive effect of nucleos(t)ide analogues on hepatocellular carcinoma recurrence in patients who underwent curative treatments

Ref.	No. of studies	No. of patients (T/C)	OR (95%CI)	P
Miao <i>et al</i> ^[98]				
1 yr recurrence	2	119 (46/73)	0.59 (0.24-1.43)	0.24
2 yr recurrence	2	119 (46/73)	0.82 (0.34-1.74)	0.60
Wong <i>et al</i> ^[65]	9	555 (204/347)	0.59 (0.35-0.97)	0.04
Sun <i>et al</i> ^[78]	13	6350 (1227/5123)	0.66 (0.54-0.80)	< 0.0001
Zhou <i>et al</i> ^[79]	8	6127 (NS)	0.69 (0.59-0.80)	< 0.00001

NS: Not significant; T: Treatment group; C: Control group.

occurs in almost all patients after liver resection and can severely reduce liver function and survival^[68]. Initial studies with small sample sizes did not find any significant effect of NAs to prevent HCC recurrence^[69-71]. In the first study that demonstrated a beneficial effect, Kubo *et al*^[72] found a lower 5-year disease-free survival rate after surgery in the lamivudine-treated group than control group. Subsequent studies provided conflicting results most probably due to the insufficient number of patients included, treatment heterogeneity (resection, local ablation, chemoembolization), and short duration of follow-up after resection (Table 3). For example, Chan *et al*^[73] reported a significantly higher 5-year tumor-free survival rates in the treatment group (42 patients, lamivudine 100 mg/d or entecavir 0.5 mg/d) than in the control group (94 patients) (51.4% vs 33.8%, respectively, $P = 0.05$). In contrast, Li *et al*^[74] demonstrated a higher but insignificant 1-year tumor free survival after curative hepatectomy in treated (Lamivudine ± adefovir) vs control groups (23.3% vs 8.3%, respectively, $P = 0.072$). Yet, the duration of follow-up after resection was too short to get conclusions. A larger study with a longer duration of follow-up in a retrospective nationwide cohort by Wu *et al*^[75] demonstrated a significantly reduced HCC recurrence rate in patients receiving NAs after liver resection. Two recently published randomized-controlled trials and several meta-analyses (Table 4) also confirmed these results which were obtained from retrospective cohort studies^[65,76-79].

CONCLUSION

In terms of HBV and hepatocarcinogenesis, it is important to emphasize that unlike other chronic liver diseases, HCC is not always seen on a background of advanced fibrosis or cirrhosis in CHB patients. Many studies confirmed the concept of suppression of HBV replication for chemoprevention of HCC in either primary or secondary prevention settings. Many of those studies are not perfect, but cumulative evidence shows an undeniable beneficial effect of NAs. Although the effect of modern NAs cannot be assessed in prospective-controlled trials which include placebo-treated or untreated patients in the control groups, there is no doubt that entecavir or tenofovir can provide greater and

long-term virological suppression leading to reduced HCC incidence and better patient survival. Regardless of the antiviral treatment, several risk factors including but not limited to old age, male gender, longer duration of the disease, inadequate virological suppression and presence of cirrhosis are clearly associated with the ongoing risk of HCC development. Fortunately, inadequate virological suppression is not an issue with the newer antivirals, if patients are adherent with their medications. Recent evidence also shows that treatment with NAs cannot completely wipe out the risk of HCC, even in patients without risk factors or patients who clear HBsAg. Therefore, future studies should focus on differentiating patients who remain under risk despite effective antiviral therapy and providing cost-effective surveillance strategies in those patients under risk of HCC.

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