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TOPIC HIGHLIGHT

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Hepatocellular carcinoma in chronic hepatitis B patients under antiviral therapy

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Abstract

Patients with chronic hepatitis B are at increased risk of hepatocellular carcinoma (HCC), while the inhibition of viral replication can represent a reasonable target for HCC prevention. Interferon-α therapy results in decreased HCC risk, which is more evident in patients with high baseline HCC risk. The majority of chronic hepatitis B patients are treated with a nucleos(t)ide analogue (NA) for several reasons including the non-sustained response after interferon-α. The effect of the first licensed and low genetic barrier NA, lamivudine, on HCC incidence, has been repeatedly evaluated. Lamivudine, compared to no treatment, reduces the HCC incidence, which may increase again in cases with lamivudine resistance. Emerging data with the currently first-line NAs, entecavir and tenofovir, suggest that they also reduce the HCC incidence. The treatment benefit in reduction of the HCC incidence is always greater in patients with high baseline HCC risk, particularly cirrhotics, and without virological remission under entecavir/tenofovir. However, the HCC risk is not eliminated even in the vast majority of patients who remain in virological remission under entecavir/tenofovir. Therefore, patients at increased baseline HCC risk should continue to undergo HCC surveillance even if they have achieved complete long-term inhibition of viral replication and improvements in liver histology.

Key words: Chronic hepatitis B; Hepatocellular carcinoma; Interferon; Lamivudine; Adefovir; Entecavir; Tenofovir; Virological remission; Cirrhosis

Core tip: Antiviral therapy reduces but does not eliminate the risk of hepatocellular carcinoma (HCC) in chronic hepatitis B patients with or without cirrhosis. The reduction of the HCC incidence under a high genetic barrier nucleos(t)ide analogue is higher in the vast majority of patients who will achieve virological remission compared to those who may maintain detectable viral replication. In current clinical practice, however, patients at increased baseline HCC risk should continue to undergo HCC surveillance according to the existing recommendations even if they have achieved complete long-term inhibition of viral replication and improvements in liver histology.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer death[1]. It represents more than 90% of primary liver cancers and is a major global health problem. In most

cases, HCC develops within an established background of chronic liver disease. Following this, chronic hepatitis B virus (HBV) infection is a significant predisposing factor for the development of HCC and accounts for more than 50% of all cases[2]. The relative risk of HCC development is 100-fold higher for patients chronically infected with HBV versus those who are not infected. The risk is even higher for cases with high viral replication and/or HBV related cirrhosis[3].

In patients with cirrhosis, surveillance for HCC increases the possibility of an earlier diagnosis and improved survival[1]. However, screening programs are rather unsatisfactory and the prognosis remains poor because therapeutic interventions are rather ineffective in advanced stages[4]. Therefore, the development of preventive strategies is mandatory. HCC related to HBV can be prevented by vaccination. Nationwide vaccination of infants in Taiwan reduced the incidence of HCC in children aged 6-9 years from 0.52 per 100.000 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986[5]. Nevertheless, the incidence of HCC is expected to increase during the next years because approximately 400 million people who are already chronically infected with HBV cannot benefit from immunization[6]. In patients with chronic HBV infection and high serum HBV DNA levels, viral replication can be inhibited by antiviral agents that prevent the progression of liver disease and perhaps the development of HCC in the long-term.

The current therapeutic options for patients with chronic hepatitis B include treatment with standard or PEGylated interferon-α (IFN-α), a drug with antiviral, immunomodulatory and perhaps antitumoral activities, and five oral nucleos(t)ide analogues (NAs) (lamivudine, adefovir, entecavir, telbivudine, tenofovir)[7]. In this review, we summarize the data on the impact of antiviral treatment in the prevention of HCC in patients with chronic HBV infection.

RATIONALE OF ANTIVIRAL TREATMENT FOR HCC PREVENTION

It is believed that persistent viral replication together with the resulting liver injury are key risk factors for HBV-related HCC[8,9]. More specifically, a direct linear relationship was reported between viral load and HCC risk[10]. Chronic HBV infection promotes viral induced immune response with release of cytokines and genotoxic reactive oxygen species leading to liver cell necrosis as well as to activation of liver fibrosis cascade. The ensuing acceleration of hepatocyte cell cycles and the increased risk of genetic alterations might culminate in malignant transformation of hepatocytes[11].

Moreover, the HBV sequences can integrate into cellular DNA and may modulate the expression of neighboring cellular genes in a cis-acting way[12]. The integration of HBV DNA may cause overexpression of those cellular genes which in turn contributes to the development of carcinogenesis[13,14]. Furthermore, the viral protein HBx may play a crucial role in hepatocarcinogenesis because its trans-activation is involved in the function of a large number of signaling pathways and cellular genes that are involved in oncogenesis, proliferation, inflammation and immune responses[15]. Since all of the above mechanisms require the presence and replication of the virus, suppression of viral replication seems to be a reasonable target for the prevention of HCC.

There are additional important viral and host factors that may affect the risk of HCC development. Adequate evidence suggest that HBV genotype C is associated with more active and rapidly progressive liver disease including more frequent HCC development, compared to genotype B[16]. HBV genome mutations such as pre-S deletions, enhancer II mutations (T1653) and core promoter mutations (V1753, T1762 and A1764) have also been found to be associated with a higher HCC risk[17,18]. Moreover, older age, male gender, alcohol abuse and possibly metabolic syndrome also increase the risk of HCC[19,20].

Lastly, recent data from Eastern Asia showed that high levels of HBV surface antigen (HBsAg) (> 1000 IU/mL) in HBV e antigen (HBeAg) negative patients with low levels of HBV DNA (< 2000 IU/mL) is an independent risk factor for HCC development[21]. As HBsAg is mainly produced by the integrated form of HBV DNA, low viremic patients who have high HBsAg level might harbor more hepatocytes with HBV integration thus increasing genomic instability which play an important role in carcinogenesis.

IFN-α AND HCC

The usefulness of IFN-α in the prevention of HBV-related HCC has been investigated only with traditional IFN-α to date, as PEGylated IFN-α was licensed relatively recently and long-term follow-up studies have not been published yet. The IFN-α data on HCC prevention in patients with chronic hepatitis B have been conflicting so far and thus several meta-analyses have tried to elucidate this issue (Table 1). The first meta-analysis of 7 studies (2 Oriental-5 European) including 1505 patients with cirrhosis suggested a decreased incidence of HCC in IFN-α-treated patients (risk reduction-6.4%, $P < 0.001$)[22]. However, the pooled estimate in favor of IFN-α was a consequence of the two Oriental trials because the subgroup analysis of the five European studies found no benefit from IFN-α on the prevention of HCC (risk reduction-4.8%, NS). Sung *et al*[23] performed a meta-analysis of 12 randomized, case-control and cohort studies (1292 IFN-α treated and 1450 untreated patients) and showed that the HCC risk was reduced by 34% in IFN-α treated patients (RR = 0.66, 95%CI: 0.48-0.89). Subgroup analysis revealed a significant benefit in patients with early cirrhosis (RR = 0.53, 95%CI: 0.36-0.78) but not in patients without cirrhosis (RR = 0.72, 95%CI: 0.16-3.15). In addition, no difference was found in the HCC incidence in relation to virological response to therapy (RR = 0.76,

Table 1 Summary of meta-analyses evaluating the effect of antiviral treatment on the incidence of hepatocellular carcinoma in patients with chronic hepatitis B

1st author, year	No. of studies, total (used[1])	Total No. of patients, treated/ untreated	Treatment regimen	HCC cases, total *n*	HCC incidence	RD or RR	95%CI	*P* value
Cammà *et al*[22], 2001	7	853/652	IFN-α	122	Overall	RD = -6.4	-2.8--10	< 0.001
	(5)				European studies	RD = -4.8	-11.1-1.5	NS
	(2)				Oriental studies	RD = -8.0	-1.4--14.6	< 0.001
Sung *et al*[23], 2008	12	1292/1458	IFN-α	190	Overall	RR = 0.66	0.48-0.89	0.006
	(6)				Cirrhotics	RR = 0.53	0.36-0.78	0.001
	(3)				Non-cirrhotics	RR = 0.72	0.16-3.15	NS
	(4)				Virological responders	RR = 0.76	0.08-7.23	NS
	(4)				Non-virological responders	RR = 0.64	0.33-1.26	NS
Yang *et al*[24], 2009	11	1006/1076	IFN-α	178	Overall	RR = 0.59	0.43-0.81	0.001
Miyake *et al*[25], 2009	8	553/750	IFN-α	100	Overall	RD = -5.0	-9.4--0.5	0.028
	(3)				European studies	RD = -0.5	-4.9-4.0	NS
	(5)				Asian studies	RD = -8.5	-13.6--3.6	0.001
	(5)				Incidental rate of HCC ≥ 10%	RD = -9.4	-14.2--4.6	< 0.001
	(3)				Incidental rate of HCC < 10%	RD = -0.2	-4.3-4.7	NS
	(4)				HBeAg positive ≥ 70%	RD = -6.0	-11.8--0.2	0.043
	(3)				HBeAg positive < 70%	RD = -5.4	-15.4-4.6	NS
Sung *et al*[23], 2008	5	1267/1022	LAM	152	Overall	RR = 0.22	0.10-0.50	< 0.001
	(3)				Cirrhotics	RR = 0.17	0.04-0.79	0.020
	(2)				Non-cirrhotics	RR = 0.21	0.10-0.47	< 0.001
	(3)				Drug resistance	RR = 0.52	0.28-0.97	0.040
	(3)				Without drug resistance	RR = 0.37	0.17-0.77	0.008
	(3)				HBeAg positive	RR = 0.21	0.10-0.44	< 0.001
	(3)				HBeAg negative	RR = 0.25	0.06-1.06	NS
Papatheodoridis *et al*[38], 2010	21 (3)	3881/534	LAM	202	Treated *vs* untreated	2.8% (22/779) *vs* 6.4% (34/534)		0.003
	(3)				Treated in remission *vs* untreated	2.5% (9/353) *vs* 6.4% (34/534)		0.015
	(3)				Treated without remission *vs* untreated	2.8% (12/426) *vs* 6.4% (34/534)		0.016
	(10)				Treated in remission *vs* treated without remission	2.3% (23/982) *vs* 7.5% (64/852)		< 0.001
	(14)				Treated in remission under initial therapy *vs* treated in remission under rescue therapy	2.3% (23/982) *vs* 5.9% (19/320)		0.003
Singal *et al*[49], 2013	49 (6)	10025/3571	LAM or Other NAs[3]	808	LAM[2] *vs* untreated	RR = 0.48	0.38-0.61	< 0.001
	(49)				No difference between NAs[3]	Pooled HCC incidence rate: 1.3 (1.1-1.6) per 100 person-years		

[1]Number of studies included in each analysis; [2]In 6 studies including both LAM treated (*n* = 3306) and untreated patients (*n* = 3571); [3]In the 49 studies, there were 5946 patients treated with LAM, 1929 patients treated with adefovir, 879 patients treated with entecavir, 616 patients treated with telbivudine and 657 patients treated with tenofovir. IFN-α : Interferon-α; LAM: Lamivudine; NS: Non-significant.

95%CI: 0.08-7.23). In a more recent meta-analysis involving 11 studies (1006 IFN-α treated and 1076 controls), IFN-α reduced the risk of HCC in chronic hepatitis B patients by 41% compared to untreated controls[24]. Finally, Miyake *et al*[25] included 8 studies in a meta-analysis and found a preventive effect of treatment in favor of IFN-α (risk difference, -5.0%, $P = 0.028$) that was more pronounced in Asian patients, in patients with a baseline HCC risk (HCC risk in untreated cohorts) > 10% and in HBeAg positive patients (Table 1).

According to the aforementioned meta-analyses, IFN-α therapy appears to decrease the incidence of HCC, particularly in patients at high baseline risk for HCC development. It should be noted that the results of the individual studies should be interpreted with caution, as they were usually underpowered to capture relatively infrequent hard end-points such as HCC and they often tended to enroll subjects with less severe disease with low HCC risk. The effectiveness of IFN-α treatment was more evident in HBeAg positive patients suggesting that IFN-α may reduce the HCC risk more easily in patients with high viral replication and perhaps without HBV DNA integration into the host genome by accelerating the HBeAg seroconversion phase. There are no data on the impact of IFN-α-induced HBV DNA elimination in the reduction of HCC risk. In any case,

most of the patients with sustained response to IFN-α still have detectable HBV DNA by sensitive polymerase chain reaction (PCR) assays. However, residual viraemia in the absence of biochemical evidence of necroinflammatory liver activity seems to be of no clinical relevance, as the achievement of sustained biochemical remission in HBeAg negative patients has been associated with a significant decrease of the HCC incidence[26]. It should be noted that less than 30%-35% of patients who receive IFN-α achieve sustained responses[7,27,28]. Moreover, patients with advanced cirrhosis may experience severe liver decompensation during treatment with IFN-α[7,28]. Therefore, patients with contraindications to IFN-α including advanced liver disease as well as cases who do not achieve sustained off-treatment response after a course with IFN-α should receive therapy with a NA[7,28].

NAS AND HCC

Most patients are currently treated with oral NAs. These agents represent the first-line treatment option for the majority of chronic hepatitis B patients because of the relatively low efficacy and possible contraindications for or poor tolerance of IFN-α. In addition, they are used even in the majority of patients who may start with standard or recently PEGylated IFN-α and fail to achieve a sustained response[7,29,30]. Long-term therapy with NAs has improved the overall outcome of chronic hepatitis B and resulted in a substantial reduction in the need for liver transplantation[31]. The third generation NAs, entecavir and tenofovir, are currently recommended by the main treatment guidelines as the first-line NAs options[7,29,30] due to their high potency and high genetic barrier. Long-term monotherapy with entecavir or tenofovir achieves maintained on-therapy complete viral suppression in the vast majority of patients (> 95%), progressively increasing rates of HBeAg seroconversion in HBeAg positive cases and improvement of liver histology including reversion of histological cirrhosis in most cases[32-36]. Nevertheless, the effect of NAs on the prevention of HBV-related HCC is still unclear.

LOW-MODERATE GENETIC BARRIER NAS

Most of the published data on the effects of NAs on the HCC risk are derived from studies using lamivudine. In the only randomized, controlled clinical trial including 651 chronic hepatitis B patients (58% HBeAg positive) with biopsy-proven cirrhosis or advanced fibrosis, lamivudine was found to significantly reduce the risk of HCC compared to placebo (3.9% *vs* 7.4%, $P = 0.047$)[37]. When HCC cases diagnosed during the first year of treatment were excluded, the risk reduction was marginally non-significant ($P = 0.052$). It should be noted that the study was terminated early (after a mean duration of 32.4 mo) because of significant beneficial effects in the treatment group (7.8% developed cirrhosis complications *vs* 17.7% in the placebo group, $P = 0.001$). Therefore, it could be argued that the early termination of the study probably made the effect of HCC prevention less obvious.

Sung *et al*[23] performed a meta-analysis of 5 studies involving 1267 treated patients (mostly with lamivudine) and 1022 controls (Table 1). They showed that the use of NAs reduced the HCC incidence by 78% (2.5% for NAs *vs* 11.7% for controls; RR = 0.22, $P < 0.001$). The HCC risk was found to be significantly reduced in patients with cirrhosis (NAs: 3.9% *vs* untreated controls: 22.4%; RR = 0.17, $P = 0.02$), in patients without cirrhosis (NAs: 1.8% *vs* untreated controls: 8%; RR = 0.21, $P < 0.001$) and even to patients who developed viral resistance (NAs: 3.3% *vs* untreated controls: 6.4%; RR = 0.52, $P = 0.04$). In addition, significantly lower HCC rates reported in treated than untreated HBeAg positive patients (1.7% *vs* 7.9%, $P < 0.001$), while there was only a numerical trend for reduced HCC rates in treated compared to untreated HBeAg negative patients (3% *vs* 10.5%, $P = 0.06$).

Papatheodoridis *et al*[38] performed another systematic review including randomized or observational cohort studies of adult patients with chronic hepatitis B and/or cirrhosis who received treatment with lamivudine and/or perhaps adefovir for a mean/median duration of ⩾ 24 mo (Table 1). Twenty-one relevant studies (16 with NAs naïve patients-5 with lamivudine resistant patients) were identified including 3881 CHB patients (33% cirrhotics, 49% HBeAg positive). In the analysis of the 3 studies including both treated and untreated patients[37,39,40], HCC was detected significantly more frequently in untreated controls (34/534 or 6.4%) than in all treated patients (22/779 or 2.8%, $P = 0.003$) or in treated patients remaining in virological remission (9/353 or 2.5%, $P = 0.015$) or in treated patients with virological breakthroughs or no response (13/426 or 3%, $P = 0.016$). In the 16 studies including NAs naïve patients, the incidence of HCC was found to be higher in patients with than without cirrhosis (10.8% *vs* 0.5%, $P < 0.001$) and in patients with virological non-response or breakthroughs than in patients remaining in virological remission (7.5% *vs* 2.3%, $P < 0.001$). A higher incidence of HCC was also reported in studies with than those without regular HCC surveillance (6.6% *vs* 2.3%, $P < 0.001$), in studies including patients with a mean/median age ⩾ 50 than < 50 years (6% *vs* 2.8%, $P < 0.001$) and in studies with predominantly (> 85%) HBeAg negative than predominantly HBeAg positive patients (5.5% *vs* 0.5%, $P < 0.001$).

In the 5 studies including patients with lamivudine resistance[38], HCC developed exclusively in cirrhotics (17.6% *vs* 0%, $P < 0.001$) and more frequently in patients with persistent viremia than in those who achieved virological remission (20.2% *vs* 5.9% $P < 0.001$). However, the induction of virological remission after rescue therapy was not found to be associated with a decreased HCC risk after the exclusion of 13 patients who had already developed HCC at the onset of the adefovir rescue therapy (5.9% *vs* 8.8%, $P = 0.466$). The cumulative HCC rate was significantly higher in patients with lamivudine resistance than in naïve patients regardless of liver disease

severity (7.1% *vs* 3.8%, $P = 0.001$) or among cirrhotics (17.6% *vs* 10.8%, $P = 0.015$).

In a more recent large Greek cohort study published after the latter meta-analysis, 818 HBeAg negative chronic hepatitis B patients with or without cirrhosis starting with lamivudine monotherapy were included[41]. During a median follow-up of 4.7 years, the HCC incidence was again higher in older patients and those with cirrhosis at baseline, but virological on-therapy remission was not found to decrease the incidence of HCC in all patients ($P = 0.322$) or in patients with cirrhosis ($P = 0.327$), while there was a trend for lower incidence in non-cirrhotic patients with than without maintained on-therapy remission ($P = 0.076$). In contrast, in another recent Japanese cohort study, maintenance of virological remission under lamivudine was reported to achieve significant reduction in the HCC incidence[42]. These seemingly conflicting results may be due to differences in patient characteristics (Caucasian or Asian patients, predominance of HBeAg negative or HBeAg positive patients, older or younger ages) as well as due to differences in the management of lamivudine resistance (prompt or no rescue therapy).

Despite the limitations of most cohort studies including heterogeneous patient populations, variations in treatment regimens and patient monitoring, differences in the definitions of response, wide range in the sensitivity of HBV DNA assays and different durations of follow-up, it is now widely accepted that even the administration of lamivudine, a low genetic barrier NA, significantly reduces the risk of HCC particularly in patients with cirrhosis and in those who achieve maintained virological remission. However, the risk of HCC remains high in patients with cirrhosis even if they achieve virological remission, particularly at older ages[2,4,38]. In addition, development of lamivudine resistance appears to be associated with an increased risk of HCC, which may not be reduced by an effective rescue therapy. The latter data in combination with the very high and progressively increasing rates of lamivudine resistance further discourage the use of lamivudine as first-line option for the treatment of chronic hepatitis B[7,29,30].

HIGH-GENETIC BARRIER NAS

There are only a few recent retrospective or prospective observational cohort studies that provide HCC data for patients treated with the high-genetic barrier NAs. Most of the available studies include patients treated with entecavir and only one patients treated with tenofovir that has been available in chronic hepatitis B for a shorter period.

In a retrospective study from Japan, Hosaka *et al*[43] compared the incidence of HCC in entecavir treated patients with a historical cohort of untreated HBV patients. They used a propensity score matching to eliminate the baseline differences resulting in a sample size of 316 patients per cohort (27% cirrhotics). The cumulative HCC incidence at 5 years was significantly lower in the entecavir treated patients than in untreated controls (3.7% *vs* 13.7%, $P < 0.001$). Cox regression analysis showed that entecavir reduced the HCC risk by 63% (HR = 0.37; 95%CI: 0.15-0.91). However, the benefit of entecavir in the reduction of cumulative HCC risk was significant only in cirrhotics (7% *vs* 39%, $P < 0.001$) but not in non-cirrhotics (2.5 *vs* 3.6%, $P = 0.440$).

The favorable effect of treatment with the high-genetic barrier NAs on the risk of HCC was also confirmed in other studies. Wong *et al*[44] performed a retrospective-prospective cohort study including 1446 NAs naïve or NAs experienced (28%) patients treated with entecavir and 424 historical untreated controls. Overall, there was no significant difference in the HCC rates between the entecavir treated patients and untreated controls. However, among patients with cirrhosis, entecavir significantly reduced the incidence of HCC compared to untreated cirrhotics (13.8% *vs* 26.4%, $P = 0.049$), while no difference was found in non-cirrhotics (3.3% *vs* 3.0%, P = non-significant).

In another study, Kim *et al*[45] used a prediction model to compare the incidence of HCC in 641 patients treated for 6 years with tenofovir in the tenofovir long-term registration trial with the predicted HCC rate estimated by the REACH-B risk calculator. The authors found that tenofovir reduced the HCC incidence compared to the predicted HCC risk. Specifically, there was a progressive divergence between the predicted and observed number of HCC cases after 3.3 years of follow-up with a standardized incidence ratio of 0.55 (95%CI: 0.32-0.94) at the latest follow-up (median: 5.52 years).

All the data summarized above show that treatment with a high-genetic barriers NA reduces the risk of HCC compared to no treatment with a more profound effect in cirrhotics. The lower benefit on the HCC risk in non-cirrhotic patients seems to be reasonably related to the low baseline HCC risk in this sub-group of patients. Therefore, great numbers of patients and long follow-up periods are required to provide the studies including non-cirrhotic patients with the appropriate power in order to detect a potential benefit on the HCC incidence from these agents.

The effect of entecavir on the risk of HCC has also been compared to the effect of lamivudine in some studies. In the study from Japan by Hosaka *et al*[43], the HCC incidence in the entecavir treated patients was compared to that in a historical cohort of 182 patients treated with lamivudine monotherapy without any rescue therapy in case of resistance. The reduction in the HCC incidence was greater in the entecavir treated than in non-rescued lamivudine treated cirrhotic patients (7% *vs* 22%, $P = 0.043$) but such an effect was not seen in non-cirrhotics (2.5% *vs* 4.9%, $P > 0.05$). On the contrary, an advantage of entecavir over lamivudine in the reduction of HCC risk was not confirmed in other studies. In a prospective study from Japan as well, Kobashi *et al*[46] assessed the incidence of HCC in 129 naïve patients (22% cirrhotics) treated with entecavir and 127 patients (27% cirrhotics) treated with lamivudine. After a mean follow-up of 4.25

years, HCC developed in 35 patients (11 on entecavir and 24 on lamivudine) with the 5-year cumulative HCC incidence being similar (12.4%) in the two groups (P = 0.680). Lamivudine resistance was developed in 60 (47%) of the 127 lamivudine treated patients and was associated with a significantly increased risk of HCC compared to patients without lamivudine resistance (P = 0.035). In a large nationwide prospective cohort study from Greece, Papatheodoridis *et al*[47] estimated the incidence of HCC in 321 HBeAg negative chronic hepatitis B patients (25% cirrhotics) treated with entecavir (86% naïve, 14% experienced) and compared it with the HCC incidence in a historical cohort of 818 patients treated with lamivudine and perhaps adefovir upon lamivudine resistance (26% cirrhotics). After a mean follow-up of 30 mo, 1.2% (4/321) of entecavir treated patients developed HCC with a trend for lower 5-year cumulative HCC incidence in the entecavir compared to the lamivudine group (4.8% *vs* 5.6%, P = 0.096). In the multivariate analysis, however, the HCC risk was independently associated with older age, male gender and cirrhosis but not with type of initial therapy. Finally, in a relatively small study from Turkey, Köklü *et al*[48] retrospectively analyzed the data from 227 patients (86% naïve, 14% experienced) with HBV cirrhosis (46% decompensated) who were treated with tenofovir (n = 72, 36% decompensated), entecavir (n = 77, 47% decompensated) or lamivudine (n = 74, 54% decompensated). The incidence of HCC was not statistically different between patients treated with newer antivirals (entecavir/tenofovir: 4% after 2 years of follow-up) and those treated with lamivudine (9% after 3 years of follow-up).

Given that the newer high-genetic barrier NAs achieve more potent and durable suppression of HBV replication and that lamivudine resistance has been associated with an increased risk of HCC, one would expect an advantage over lamivudine in the prevention of HCC development. However, the data from the currently available studies are limited and the findings appear to be inconsistent. Only one study reported a significant benefit in the reduction of the HCC incidence from entecavir over lamivudine without any rescue therapy upon resistance[43]. In contrast, three other studies and a recent meta-analysis reported no difference in the HCC rates between entecavir and lamivudine treated patients (Table 1)[46-49]. All these findings should be seen with caution, as they come from studies with low statistical power or different strategies for the management of lamivudine resistance (no rescue therapy, perhaps delayed rescue therapy, prompt onset of rescue therapy) that may be critical for the HCC risk. Moreover, these comparisons have limited practical value, as a high-genetic barrier NA should be used in any chronic HBV patient anyway because of their high potency and negligible risk of long-term resistance[7,28].

Other studies usually including NAs naïve and NAs experienced patients assessed the impact of entecavir on HCC development according to the induction of virological remission. Yang *et al*[50] investigated the risk of HCC in 487 chronic hepatitis B patients (34% NAs experienced, 40% cirrhotics) treated with entecavir for ⩾ 12 mo. HCC developed in 36 patients (7.4%). The risk of HCC was lower in patients with than without virological remission in both cirrhotics (HR = 0.21, 95%CI: 0.07-0.60) and non-cirrhotics (HR = 0.08, 95%CI: 0.01-0.50). In a multicenter European cohort (VIRGIL) study[51] including 372 entecavir-treated patients (26% cirrhotics, 63% NAs experienced), virological remission reduced the probability of a clinical event (HCC, hepatic decompensation or death) by 71% (HR = 0.29, 95%CI: 0.08-1.00, P = 0.05). The benefit of virological remission was significant only in patients with cirrhosis (HR = 0.22, 95%CI: 0.05-0.99, P = 0.04). Lastly, Kim *et al*[52] assessed the risk for development of HCC in 324 entecavir treated patients with HBV cirrhosis (32% decompensated). The 5-year cumulative incidence of HCC was 28.5% and patients with virological remission had significantly lower probability for development of HCC (RR = 0.056, P < 0.001).

There is a considerable amount of evidence that suppression of viral replication improves the outcome of chronic hepatitis B patients[7,29,30]. Since the risk of HCC is related to the viral load, reduction of viral load with therapy should presumably reduce the incidence of HCC[10]. This hypothesis is further supported by the results of the above single-arm studies in which long-term virological remission under entecavir was associated with a significant decrease in the incidence of HCC[50-52]. Again, the benefit on the reduction of the HCC incidence was more obvious in patients with cirrhosis who are at a high HCC risk if they remain untreated.

CONCLUSION

It is currently clear that antiviral therapy reduces but does not eliminate the risk of HCC in chronic hepatitis B patients with or without cirrhosis. Based on the standard IFN-α data, the currently used PEGylated IFN-α is also expected to reduce the incidence of HCC. Patients without a sustained off-treatment response after (PEGylated) IFN-α therapy should be treated with a NA, which represents the treatment option for the majority of chronic hepatitis B patients for several reasons[7,28]. Many data have shown that even treatment with lamivudine reduces the incidence of HCC, which may increase again in cases with untreated lamivudine resistance. Emerging data with the currently first-line NAs, entecavir and tenofovir, suggest that the risk of HCC is also reduced under long-term therapies with these agents. The treatment benefit in the reduction of the HCC incidence is always greater in patients with high baseline HCC risk, particularly those with cirrhosis. In addition, the reduction of the HCC incidence under a high genetic barrier NA is higher in the vast majority of patients who will achieve virological remission compared to those who may maintain detectable viral replication. Whether therapy with a high-genetic barrier NA offers an additional benefit on the reduction

of the HCC incidence compared to other NAs with low-moderate genetic barriers remains unclear, but it has no particular clinical interest, as monotherapy with entecavir and tenofovir represent the first-line NA choice for chronic hepatitis B patients anyway due to superiority of these agents in potency and resistance profile[7,28,32-36].

Since the risk of HCC is not eliminated even in patients who remain in virological remission under a high-genetic barrier NA, it has been suggested that HBV DNA might have already been integrated into the host genome before the onset of treatment resulting in genomic alterations and/or chromosomal instability[53]. Thus, the oncogenic process may have started before therapy and the liver may contain clones of cells carrying genetic abnormalities that predispose to cancer[54]. Given that the duration of most studies with the high-genetic barrier NAs does not exceed 4-6 years, it remains to be seen whether the HCC incidence will remain stable over time after 5-6 years of NA therapy. In current clinical practice, however, patients at increased baseline HCC risk should continue to undergo HCC surveillance according to the existing recommendations even if they have achieved complete long-term inhibition of viral replication and improvements in liver histology.

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