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Role of Anti-Viral Therapy on Hepatitis B Virus (HBV)-Related Hepatocellular Carcinoma (HCC)

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Additional information is available at the end of the chapter

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1. Introduction

Chronic hepatitis B virus (HBV) infection is a major global healthcare problem affecting around 350 million people. It can cause various complications including liver failure, hepatic decompensation and hepatocellular carcinoma (HCC), which lead to significant morbidity and mortality with more than 1 million deaths annually [1].

2. Epidemiology

HCC is one of the most common solid tumors worldwide. It is the fifth commonest cancer with more than 600 000 new cases per year. [2,3] It has been estimated that about 18,000 deaths occurred in the United States in 2008 because of cancer of the liver and intrahepatic bile ducts (mostly HCC), with a strong male preponderance as in Asian studies. [4] Although a certain proportion of these cases have been attributed to hepatitis C viral infection, it may be, at least in part, due to an increase in HBV-related HCC, particularly among immigrants from countries with high rates of endemic infection.

Many cohort studies in Asia have confirmed the high risk of HCC in HBsAg-positive individuals. [5,6] In a Chinese cohort with about 11,000 HBsAg-positive subjects followed over a mean period of 8 years, the relative risk of HCC in HBsAg-positive persons compared to HBsAg-negative controls was 18.8 for men and 33.2 for women. [6]

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On the other hand, a long-term follow-up Italian study of apparently healthy blood donors found that only 0.6% of HBsAg-positive individuals developed HCC over an average period of follow-up of 29 years, which was no different from the 0.6% rate of HCC in a group of HBsAg-negative blood donor controls followed for a similar period of time. [7]

The reason(s) for this difference in HCC risk in HBsAg-positive individuals is not known. In general, HCC risk in HBsAg-positive individuals is determined partly by type of virus and timing of infection. In Asia, HBV infection is largely acquired by mother–child transmission while Western individuals usually acquire hepatitis B at an older age (adolescence or adult-hood through sexual contact). Hence Western cohorts likely have shorter exposure and more successful immune clearance of hepatitis B than the typical Asian cohorts. Apart from the well-known environmental factors, individual genetic susceptibility also contributes to the risk of HCC. Some rare monogenic syndromes (e.g. alpha1-antitrypsin deficiency, hemochromato-sis), as well as diseases inherited as polygenic traits (e.g. autoimmune hepatitis, a family history of HCC) are associated with a high risk of HCC. The genetic susceptibility to HCC is charac-terized by a genetic heterogeneity and caused by several unlinked single gene defects. [8]

3. Pathogenesis of HCC development in chronic HBV infection

Chronic HBV infection is the dominant cause of HCC in Asia because of the endemic status of HBV. Hepatic inflammation and cirrhosis also favor the process of carcinogenesis. The risk for HCC development is increased in patients with older age and liver cirrhosis [9]. Some viral characteristics, namely positive hepatitis B e antigen (HBeAg), high serum HBV DNA level, HBV genotypes and subgenotypes, and basal core promoter mutants, are associated with an increase risk of developing HCC. [9 – 12] The level of serum hepatitis B surface antigen (HBsAg), which is not affected by the antiviral drugs, is potentially a biomarker of viral persistence during antiviral therapy which may be a useful marker of HCC development. [13] The role of this and other biomarkers is discussed below.

3.1. Serum HBV DNA level

The risk of HCC is increased in patients with higher levels of HBV replication, one manifes-tation of which is high level of serum HBV DNA level. Several large prospective Asian studies found that high level of HBV DNA was an independent risk factor for the development of HCC. [11, 14] [Figure 1]

A famous Taiwanese REVEAL-HBV study (abbreviated from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–Hepatitis B Virus) reported that the incidence of HCC increased with the serum HBV DNA strata. Among a cohort of 3,653 patients from the community, the cumulative incidence increased from 0.74% for patients with undetectable HBV DNA (<300 copies/ml) to 13.5% for those with HBV DNA ≥ 1,000, 000 more copies/ml at a mean follow-up of 11.4 years. [14]

In another prospective cohort study involving 1,006 Chinese patients in Hong Kong, the hazard ratios for HCC were 1.62 and 2.73 in those with serum HBV DNA 4.5-6.5 log copies/ml and above 6.5 log copies/ml respectively, compared to those of low viremia (<4.5 log copies/ml). [11]
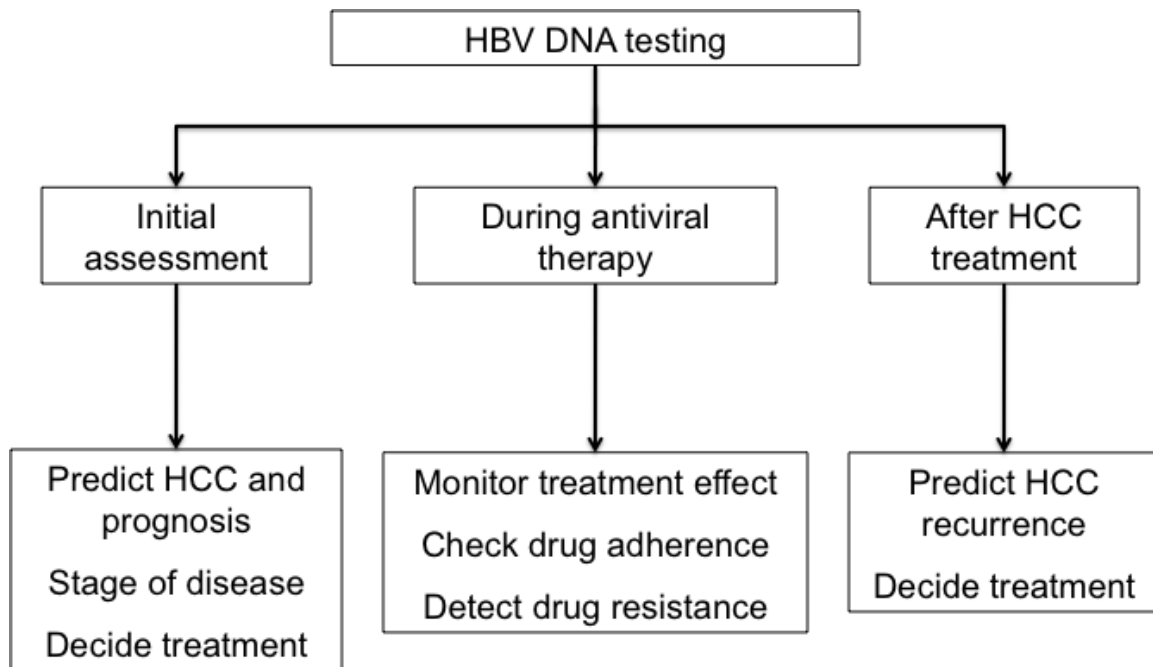

Figure 1. Role of HBV DNA testing

3.2. Hepatitis B e Antigen (HBeAg)

Hepatitis B e antigen (HBeAg) positivity is another manifestation of high levels of HBV replication. Compared to HBV non-carrier, the relative risk of HCC was increased as high as 60-fold among those positive for both HBsAg and HBeAg in a large prospective cohort study of 11 893 Taiwanese men. The relative risk was 6 times higher among HBeAg-positive patients than those who were HBeAg-negative. [10] Furthermore, clearance of HBeAg, whether spontaneous or after antiviral therapy, reduced the risk of hepatic decompensation, HCC occurrence and improved survival. [15, 16]

On the other hand, 10% to 30% of patients may still have elevated ALT and high HBV DNA levels after HBeAg seroconversion; 10% to 20% of inactive carriers may have reactivation of HBV replication and exacerbations of hepatitis after years of quiescence. [17, 18] These patients may still be at risk of HCC development.

3.3. Serum Quantitative Hepatitis B Surface Antigen (qHBsAg)

HBsAg level or qHBsAg reflects the transcriptional activity of covalently closed circular (ccc) DNA, the template for viral replication inside the nuclei of hepatocytes. [19] The combination of low serum qHBsAg and HBV DNA levels may be an accurate identification of ''true inactive carriers'' and prediction of HBsAg loss in the HBeAg-negative patients. [20] HBsAg level below

100 IU/ml can predict HBsAg loss over time in genotype B or C HBV-infected patients. [13] A recent Taiwanese study demonstrated that a high HBsAg level (≥ 1000 IU/mL) predicted the risk of HCC among patients with low serum HBV DNA level (< 2000 IU/mL). [21] In another prospective population-based cohort study with 1271 Alaskan natives with chronic HBV infection followed up for an average of 19.6 years, the incidence of HCC after clearance of HBsAg was significantly lower than the rate in those who remained HBsAg-positive. [22] However, despite the loss of HBsAg, HBV DNA was still detected in the sera of around 18% patient subjects after clearance. Hence, patients with chronic hepatitis B who have lost HBsAg can still develop HCC, even in the absence of cirrhosis. These patients should still be monitored regularly.

3.4. HBV genotypes and subgenotypes

Hepatitis B virus has been classified into at least 10 genotypes on the basis of an intergroup divergence of 8% or more in the complete genome nucleotide sequence. [23, 24] HBV subgenotypes are also identified within some genotypes such as subgenotype Ce and Cs in genotype C [11]. Compared to HBV genotype B, genotype C is associated with a 2- to 3-fold increase in risk of HCC development; [25] whereas HBV subgenotype Ce has the highest risk of HCC (hazard ratio = 2.75) and HBV subgenotype Cs has intermediate risk (hazard ratio = 1.70). [11]

One of the reasons of the increased risks in genotype C is that more patients infected with this genotype have persistently positive HBeAg and fluctuating HBeAg whereas more patients infected with genotype B HBV have persistently negative HBeAg. [25] This reflects a relatively higher level of viremia among patients infected with genotype C [26]. Due to prolonged immune clearance phase, more patients with genotype C infection eventually develop cirrhosis. [19]

The effect of genotype C and high HBV DNA level may be an independent direct pathway of hepatocarcinogenesis on top of liver cirrhosis, which is the result of continuous necroinflammation. [27] Increased cis-activation of the proto-oncogene, suppression of tumor suppressor gene, or transactivation by the HBV X protein are additional carcinogenic mechanisms. [28, 29]

3.5. Basal core promoter mutations

Basal core promoter mutations (A to T at nucleotide 1762 and G to A at nucleotide 1764), which are commonly found in HBV genotype C, may increase the risk of HCC development. [30] However, the prevalence of basal core promoter mutations increases with HBeAg seroconversion. [31, 32] In a longitudinal study of 426 patients, there was no independent association between basal core mutations and HCC development after adjustment for genotype C and serum HBV DNA level. [25]

4. Risk factors of HBV-related HCC recurrence

Although liver resection is the treatment of choice for early HCC, the 5-year overall survival after tumor resection is in the region of only 55%. [33, 34] The annual recurrence rate of HCC

is 15% to 20%, with a cumulative 5-year recurrence rate of up to 70% after curative resection. [35] High levels of recurrence after tumor resection are associated with mortality. [36]

There are two distinct types of HCC recurrence: early and late recurrence. Early recurrence describes that arising from dissemination of the primary tumor, which usually occurs within the first one to two years after the curative treatment. Early recurrence is often associated with some tumor characteristics such as multi-nodularity of the tumour and a smaller surgical margin of normal liver at the time of resection. [37]

Late recurrence is often related to the development of *de novo* HCC arising from a "field effect" in the diseased liver, which may be related to viral effects as well as the severity of liver fibrosis. [38] Hence the risk factors of late recurrence may be similar to those of HCC development, namely presence of liver cirrhosis, high serum HBV DNA level and genotype C and high alanine aminotransferase (ALT). [39-42] (Table 1)

Risk Factors for HCC Recurrence	
EARLY RECURRENCE	LATE RECURRENCE
History of Rupture	High serum HBV DNA level
Presence of lymphovascular permeation	High serum alanine aminotransferase (ALT) level
Macro- or micro-vascular invasion	Genotype C
Multifocal lesions	Liver cirrhosis
High AFP level	High Ishak hepatic inflammatory activity
Close surgical margin	High ICG-15
	Multifocal lesions

Table 1. Risk Factors for HCC Recurrence

5. Role of antiviral therapy in HBV-related HCC

Patients with HBV-related HCC suffer not only from malignancy but also chronic HBV infection. These two conditions interact with each other such that treatments for HCC may affect the activity of viral replication, whereas treatments for chronic HBV infection may influence the clinical outcome of HCC.

The association between high serum HBV load and increased risk of HCC and liver cirrhosis had been demonstrated by many studies. [14, 43] The high serum HBV DNA load is not only a key risk factor for the development and recurrence of HCC, but also the risk factor that is most amenable to control.

Antiviral therapy for HBV includes nucleos(t)ide analogs (e.g. lamivudine, adefovir, entecavir, tenofovir and telbivudine) and (peg)interferon. [44] They are all shown to achieve persistent viral suppression short term, which theoretically can retard HBV reactivation, reduce HCC occurrence and ultimately prolong patient survival.
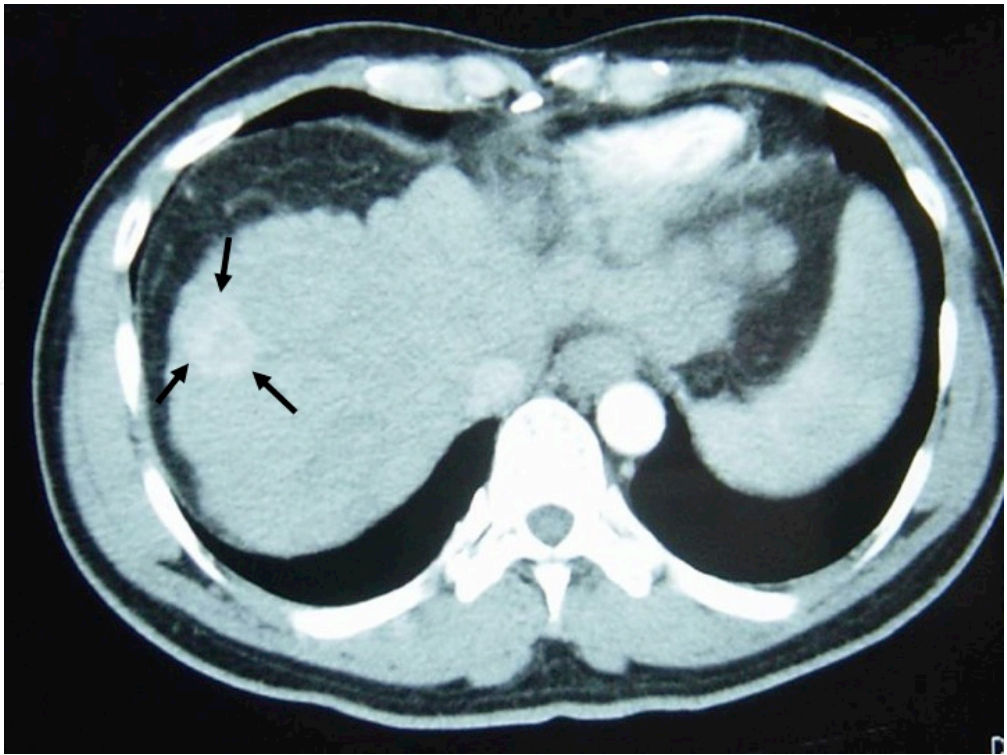
Figure 2. Computer tomography image showing a very cirrhotic liver with HCC
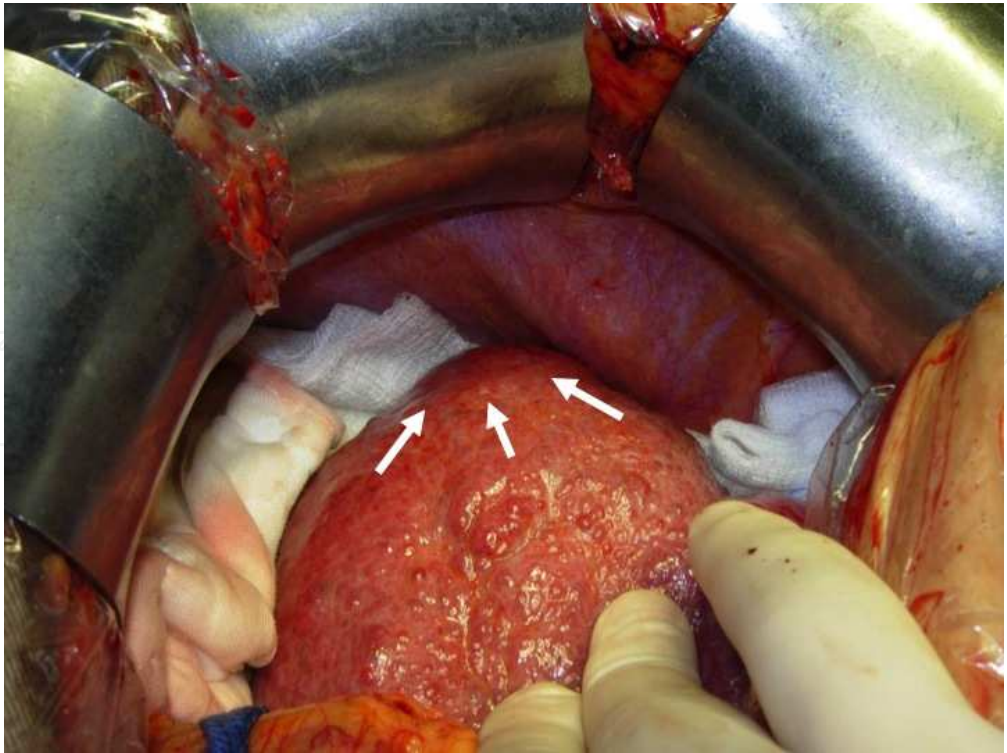

Figure 3. Intra-operative picture of a patient with HCC developed in a background of macronodular liver cirrhosis

5.1. Antiviral therapy to prevent HBV-related HCC development

High serum HBV DNA levels have been shown to be associated with an increased risk of cirrhosis and HCC. [Figure 2, 3] Moreover, in a large prospective study of more than 3000 patients with a mean follow-up of 11.4 years, Chen et al found that the incidence of HCC correlated with serum HBV DNA level at time of enrollment. Furthermore, in the sub-analysis, spontaneous decline of viremia levels was associated with a reduced risk of HCC development by comparison with patients who maintained high viremia levels. [13] In their conclusion, the authors emphasized the effective control of HBV replication with antiviral therapy in order to reduce the risk of HCC.

As persistent viral replication is associated with development of HCC, antiviral therapy effective in viral suppression may reduce HCC occurrence. Results from randomized control-led trials and multicenter retrospective studies have shown that continuous treatment with nucleos(t)ide analogues in patients with chronic hepatitis B or cirrhosis reduce the risk of HCC development. [16, 45]

Nucleoside analog lamivudine reduced the risk of HCC development by 50% compared to placebo in a randomized controlled trial involving 651 patients. [16] Unfortunately the beneficial effect of nucleos(t)ide analog may be decreased with the emergence of drug resistance mutations, namely tyrosine, methionine, aspartate (YMDD) mutations. [46] New generation nucleos(t)ide analogs of lower risk of drug resistance mutation would potentially benefit HBV-infected patients more.

Interferon-alpha (IFN-α) was the first agent approved by the Food and Drug Administration for chronic HBV infection in the 1980s. [47] Peginterferon-alpha (pIFN-α) was produced by the addition of a polyethylene glycol moiety to interferon. Consequently pIFN-α has longer half-life and higher average concentration in the body, and is now widely used due to the convenient weekly dosing. [48] Unlike oral antiviral agents, (p)IFN-α is given for finite treatment duration and administrated subcutaneously. A few meta-analyses have suggested a reduced risk of HCC and other liver-related events after (p)IFN-α treatment. [46, 48] The risk of HCC after (p)IFN-α treatment has been reportedly reduced by 34%, with the benefit is more significant among patients with early cirrhosis than among those without cirrhosis. [46]

5.2. Antiviral therapy to prevent HBV reactivation of HCC patients

Treatments for HCC, including surgical resection, local ablative therapies, transarterial chemo-embolization (TACE), may affect the activity of HBV replication, a factor that has important implications for hepatitis activity. If the treatments subsequently lead to HBV reactivation, the patient outcome may be jeopardized. [49] Most of the data on this aspect came from several studies concerning HCC patients received TACE, which involves the administration of chemotherapeutic agents targeted to the liver and raises the concern about HBV reactivation. There is a degree of inconsistency, however, with some previous studies contradicting this risk of HBV reactivation after TACE. [50, 51] A more recent study demonstrated that high-level treatment intensity, together with high HBV DNA level, was the major risk factor for HBV reactivation during TACE. [52]

HBV may also reactivate in the peri-operative period after liver resection for HCC, even among patients with relatively low HBV DNA level (<200 IU/ml). [53] This phenomenon may be explained by the fact that a single HBV DNA level at a given time is not always indicative of permanent immune-suppression of HBV replication, as indicated particularly by more recent analyses of the REVEAL data. [54]

Studies reported that an effective pre-operative anti-HBV therapy could contribute to an improvement in liver function. In a recent Chinese study, Huang et al found that hepatitis B e antigen (HBeAg) positivity, preoperative HBV-DNA above the lower limit of quantification (≥200 IU/mL), Ishak inflammation score of greater than 3, preoperative TACE, operation time of more than 180 minutes, blood transfusion, and without prophylactic antiviral therapy were significantly associated with an increased risk of HBV reactivation. More importantly, this study showed that the 3-year disease-free survival (DFS) rate and overall survival (OS) rates after resection in patients with HBV reactivation were significantly lower than those without reactivation. Another study by Thia et al reported the incidence of all causes of post-operative hepatitis and the exacerbation of chronic hepatitis B. [55] In this study, 1- and 2-year survival rates were poorest for the ECHB group at 42.9 and 21.4%, compared with those with postoperative hepatitis due to other causes at 60.3 and 45.2% and those without postoperative hepatitis at 87.7 and 73.5%, and the difference were statistically significant. As a result, the authors recommended routine prophylactic antiviral treatment before partial hepatectomy.

The use of nucleos(t)ide analogs such as lamivudine may be useful to reduce the risk of HBV reactivation related to TACE or liver resection. [53, 56]

5.3. Antiviral therapy to prevent HBV-related HCC recurrence after curative treatment

As discussed above, tumour recurrence after curative treatment of HCC was increased with the level of HBV DNA and alanine aminotransferase (ALT). [41, 42] This implies that HBV viral replication may play an important role in HCC development and high rates of viral replication are positively associated with a high risk of HCC recurrence after surgery. As antiviral therapy is effective in reducing HCC development, it is logical to believe that it can also reduce HCC recurrence after curative treatment.

Results from currently available reports were not conclusive. In a small Hong Kong study, Hung et al studied 72 patients who underwent hepatectomy for HCC and found that patients with high viral load (greater than 2000IU/mL) had a significantly higher risk of HCC recurrence after resection and viral load was the most important correctable risk factor for post-hepatectomy HCC recurrence. [40] However, the impressive result should be interpreted with caution, as the number of patients treated with antiviral therapy in this study was small.

A Korean group also reported similar findings in a cohort study of 157 patients. [57] The 5-year cumulative recurrence rates of 68 viremic patients were compared with that of another 89 non-viremic patients. The 5-year cumulative recurrence rate was significantly higher in the viremic group (73%) compared with 55% in the non-viremic group and persistent viremia was an independent risk factor for increased recurrence after surgery. The authors concluded that

antiviral therapy should be initiated in those with detectable serum HBV DNA in order to prevent long-term recurrences.

However, these results could not be reproduced in other studies. A recent comparative study by the Chinese group involving 79 patients with a median follow-up of 12 months showed no significant difference in the recurrence rate after surgery in the treatment and control group. [58] The cumulative recurrence rates of HCC did not differ significantly between a group treated with lamivudine and the control group in a Japanese study. [59] However, Kuzuya did report that all patients in the lamivudine group were able to receive curative treatment for recurrent HCC while 10 of 15 patients in the control group were unable to receive curative optimal therapy for recurrent HCC due to deterioration in remnant liver function.

Two meta-analyses have explored this issue. Miao reported that postoperative antiviral therapy as a whole has been shown to reduce HCC recurrence at year 1, 2, 3, and 5. [60] Another meta-analysis by Wong et al demonstrated that nucleos(t)ide analogue treatment was beneficial in reducing the risk of HCC recurrence after curative treatment for 41%. [61] [Table 2]

Study	Treated with antiviral		Untreated		OR, 95% C.I.
	Total	Events	Total	Events	
Li 2010	43	33	36	33	0.30 [0.08, 1.19]
Koda 2009	22	17	14	12	0.57 [0.09, 3.42]
Chuma 2009	20	8	64	22	1.27 [0.45, 3,57]
Hung 2008	10	0	62	30	0.05 [0.00, 0.90]
Yoshida 2008	33	18	71	40	0.93 [0.41, 2.13]
Kuzuya 2007	16	7	33	15	0.93 [0.28, 3.11]
Kubo 2007	14	2	10	5	0.17 [0.02, 1.16]
Shuqun 2006	16	14	17	17	0.17 [0.01, 3.73]
Piao 2005	30	14	40	26	0.47 [0.18, 1.19]

Table 2. The summary of studies comparing the effect of anti-viral treatment vs no treatment in hepatocellular carcinoma recurrence

The effect of (p)IFN-α treatment in prevention of HBV-related HCC recurrence was found controversial in a meta-analysis and systemic review. [62, 63] In addition, use of (p)IFN-α in HCC patients may be risky as they are more vulnerable to the development of hepatic decompensation with life-threatening complications including hepatic encephalopathy, ascites *etc*. [64]

In contrast, nucleos(t)ide analogues are safe and better tolerated than (p)IFN-α. Results from a randomized controlled trial [16] and multicentre retrospective study [45] have shown that continuous treatment with a nucleotide analogue in patients with chronic hepatitis B or cirrhosis can reduce the risk of HCC development.

5.4. Antiviral therapy to improve survival after curative treatment of HBV-related HCC

Antiviral treatment may render patients with HBV-related HCC able to tolerate HCC treatments better and may improve prognosis. However, the currently available studies on whether antiviral therapy is beneficial to the survival after treatment for HCC are limited.

In the Kuzuya et al study, although there was no significant difference in the survival rate between the two groups, the survival rates in the lamivudine group tended to be higher than those in the control group (p = 0.063). [59]

Similar findings were reported in a RCT by Liaw et al. [16] Although they did not show a significant effect of lamivudine on HCC recurrence, there was a significant benefit in the overall survival. They suggested that continuous treatment with lamivudine would lead to a delay in clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by a significant reduction in the incidence of hepatic decompensation and risk of HCC.

Li et al, in a recent nonrandomized study, compared the impact of antiviral treatment in 79 patients who underwent curative hepatectomy for HCC. [58] Forty-three patients received lamivudine with or without adefovir as treatment and had a significantly higher HBeAg sero-conversion rate compared with the 36 patents in the control group who received no antiviral treatment. This study showed the efficacy of post-operative antiviral therapy in suppressing viral replication and hence the authors suggested the initiation of antiviral treatment in patients with detectable serum HBV DNA level after resection. Furthermore, Li et al reported a significantly greater improvement in the residual liver volume per unit surface area at 6 months after hepatectomy in the anti-viral therapy group. [58] Remnant liver function is a major determining factor in selecting subsequent treatment for HCC recurrence and is a key prognostic factor for the overall survival. Therefore, a higher chance of receiving aggressive salvage therapy during HCC recurrence could be observed among patients receiving antiviral therapy due to better liver reserve, and resulting in a better survival. [40, 59]

The previously mentioned meta-analysis reported that antiviral therapy significantly improved overall survival, as both the mortality related to liver failure and the overall mortality were reduced. The improvement in survival was contributed to by the reduction of HCC recurrence as well as the improvement in liver function after antiviral therapy. [60] Previous studies have shown that lamivudine and telbivudine therapy could effectively suppress the HBV DNA level and improve the liver function in patients with decompensated cirrhosis. [65-67] [Table 3]

These results are particularly important because up to now, there has been no effective adjuvant treatment to prevent HCC recurrence. There is no proven role for adjuvant chemotherapy or transarterial chemo-embolization (TACE), [68] while the result for molecular targeted chemotherapy is awaited.

Although there is not enough data to suggest nucleos(t)ide analogs would reduce short-term recurrence rate or progression of disease, the enhanced post-operative viral clearance, improved residual liver volume, and promoted hepatocyte regeneration in HCC patients with

Study	Treated with antiviral		Untreated		OR, 95% C.I.
	Total	Events	Total	Events	
Li 2010	43	41	36	36	0.23 [0.01, 4.89]
Koda 2009	22	4	14	7	0.22 [0.05, 1.00]
Hung 2008	10	0	62	7	0.35 [0.02, 6.65]
Yoshida 2008	33	8	71	32	0.39 [0.15, 0.98]
Kuzuya 2007	16	0	33	6	0.13 [0.01, 2.43]
Kubo 2007	14	0	10	3	0.07 [0.00, 1.63]
Shuqun 2006	16	15	17	17	0.30 [0.01, 7.79]
Piao 2005	30	2	40	12	0.17 [0.03. 0.81]

Table 3. The summary of studies comparing the effect of anti-viral treatment vs. no treatment in the overall mortality of hepatocellular carcinoma

active hepatitis B, may significantly improve the tolerance to subsequent therapy. Hopefully, this would translate into an improvement in the overall survival.

Role of antiviral therapy as an adjuvant therapy after curative treatment of HCC should be a great topic for future studies. Further studies with more patients and longer follow-up are necessary to clarify the efficacy of antiviral treatment on HBV load and, more importantly, on survival for HBV-related HCC patients who undergo hepatectomy.

6. Drawbacks of antiviral therapy

The main drawback of the long-term use of anti-viral therapy is the emergence of drug resistance, especially for lamivudine, whose reported resistance is about 14% to 39%. [58-59, 69-70] Newer nucleotide analogues with lower resistance rates currently recommended by international guidelines may provide better viral suppression and potentially even better long-term outcomes. [71-73] Road- map models using lamivudine or telbivudine as first line agents were recently found to be a cost-effective approach for HBeAg-positive patients in Asia, while entecavir and tenofovir monotherapies were more cost-effective than the roadmap models in HBeAg-negative patients. [74] These guidelines may also be considered in HCC patients.

7. Future development

The main goal of antiviral therapy for chronic hepatitis B is to prevent the development of liver cirrhosis and HCC. Unfortunately, although many guidelines for the treatment of chronic hepatitis B have been commenced, global guideline for the use of antiviral treatment on HBV-related HCC is lacking so far. According to the American Association for the Study of Liver Diseases and Asian Pacific Association for the Study of the Liver guidelines, the factors for initiating antiviral treatments include high serum HBV DNA levels (greater than 105 copies/ml), high ALT levels (more than 2 x ULN) and presence of biopsy-confirmed liver disease or cirrhosis. [75, 76] [Table 4]

HBeAg	HBV DNA (PCR)	ALT	Recommended Treatment
Positive	≥20 000 IU/ml	≤ 2X ULN	Low efficacy with current treatment. Observe; consider treatment when ALT becomes elevated. Consider biopsy in persons ≥ 40 years, ALT persistently high normal – 2X ULN, or with family history of HCC. Consider treatment if HBV DNA ≥ 20 000 IU/ml and biopsy shows moderate/severe inflammation or significant fibrosis.
Positive	≥20 000 IU/ml	≥ 2X ULN	Observe for 3-6 months and treat if no spontaneous HBeAg loss. Consider liver biopsy prior to treatment if compensated. Immediate treatment if icteric or clinical decompensation. IFN-α / pIFN-α, LAM, ADV, ETV or LdT may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance. End-point of treatment – Seroconversion from HBeAg to anti-HBe. Duration of therapy: IFN-α: 16 weeks pIFN-α: 48 weeks LAM/ADV/ETV/LdT: minimum 1 year, continue for at least 6 months after HBeAg sero-conversion. IFN-α non-responders / contraindications to IFN-α → ADV/ETV.
Negative	≥20 000 IU/ml	≥ 2X ULN	IFN-α / pIFN-α, LAM, ADV, ETV or LdT may be used as initial therapy, LAM and LdT not preferred due to high rate of drug resistance. End-point of treatment – not defined. Duration of therapy: IFN-α/pIFN-α: 1 year LAM/ADV/ETV/LdT: ≥ 1 year IFN-α non-responders / contraindications to IFN-α → ADV/ETV.
Negative	≥2 000 IU/ml	1 - ≥ 2X ULN	Consider liver biopsy and treat if liver biopsy shows moderate/severe necro-inflammation or significant fibrosis.
Negative	≤ 2 000 IU/ml	≤ ULN	Observe, treat if HBV DNA or ALT becomes higher.
Equivocal	Detectable	Cirrhosis	Compensated: HBV DNA ≥ 2 000 IU/ml – Treat, LAM/ADV/ETV/LdT may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance. Decompensated: Coordinate treatment with transplant center, LAM (or LdT) + ADV or ETV preferred. Refer for liver transplant
Equivocal	Detectable	Cirrhosis	Compensated: Observe. Decompensated: Refer for liver transplant.

Abbreviations: ALT, alanine. aminotransferase; ULN, upper limit of normal; IFN-α, interferon alpha; pIFN-α, pegylated IFN-alpha; LAM, lamivudine; ADV, adefovir; ETV, entecavir; LdT, telbivudine

Table 4. American Association for the Study of Liver Diseases and Asian Pacific Association for the Study of Liver recommendations for treatment of chronic hepatitis B

Development of HCC is not included in the consideration of antiviral treatment. However, late recurrence is mostly due to de novo carcinogenesis associated with HBV viremia as well as the "field effect" in HBV-related HCC. The use of anti-HBV treatment as adjuvant therapy after the resection or ablation of HCC for the patients with a high HBV DNA level to prevent late recurrence should be revisited, given that the incidence of recurrence is higher than that of the initial HCC development. [77]

In the future, we look forward to more randomized studies with larger sample size, longer follow-up periods, with regular monitoring of HBV DNA. These data will help to clarify the beneficial effects of antiviral therapies in HCC, in particular if there should be a lower threshold for commencing antiviral treatment to prevent HBV-related HCC.

8. Conclusions

There is increasing evidence showing the potential beneficial effects of the antiviral therapy in reducing the HBV viral load, preventing reactivation of HBV and improving survival of HBV-related HCC patients. Anti-viral therapy with nucleotide analogues may be preferable than interferon treatment due to less adverse side effects and can be considered as a cost-effective adjuvant therapy for HCC after curative treatment. Confirmatory prospective studies with larger sample size and longer follow-up period are awaited.

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