MINIREVIEWS

Antiviral therapies for hepatitis B virus-related hepatocellular carcinoma

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Abstract

Chronic hepatitis B virus (HBV) infection is a critical risk factor for the carcinogenesis and progression of hepatocellular carcinoma (HCC). It promotes HCC development by inducing liver fibrogenesis, genetic and epigenetic alterations, and the expression of active viral-coded proteins. Effective antiviral treatments inhibit the replication of HBV, reduce serum viral load and accelerate hepatitis B e antigen serum conversion. Timely initiation of antiviral treatment is not only essential for preventing the incidence of HCC in chronic hepatitis B patients, but also important for reducing HBV reactivation, improving liver function, reducing or delaying HCC recurrence, and prolonging overall survival of HBV-related HCC patients after curative and palliative therapies. The selection of antiviral drugs, monitoring of indicators such as HBV DNA and hepatitis B surface antigen, and timely rescue treatment when necessary, are essential in antiviral therapies for HBV-related HCC.

Key words: Chronic hepatitis B; Hepatocellular carcinoma; Antiviral therapy

Core tip: This review provides an overview of recent studies and practice guidelines on antiviral treatments for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) and emphasizes their significance. HBV infection promotes HCC development by inducing liver fibrogenesis, genetic and epigenetic alterations, and the expression of active viral-coded proteins. Timely initiation of antiviral treatment is not only essential for preventing the incidence of HCC in chronic hepatitis B patients, but also important for reducing HBV reactivation, improving liver function, reducing or delaying HCC recurrence, and prolonging overall survival of HBV-related HCC patients after curative and palliative therapies.

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INTRODUCTION

Liver cancer is the fifth most common cancer in men (523000 cases/year, accounting for 7.9% of all cancers) and the seventh most common cancer in women (226000 cases/year, accounting for 6.5% of all cancers) worldwide. Hepatocellular carcinoma (HCC) is the most common form of liver cancer. Approximately 90% of HCC cases are associated with a known risk factor. According to statistics, approximately 5% of the world's population (*i.e.*, 350-400 million people) has chronic hepatitis B virus (HBV) infection, 75% of them are Asian, and approximately 60% of the HCC cases in Asia are associated with chronic HBV infection. The relative risk of HCC development is 100-fold for those who are infected with HBV *vs* those who are not. The risk is even higher for those with HBV infection and cirrhosis. A longer duration of infection and an increased degree of viremia also increase the rate of HCC occurrence. The incidence of HCC in subjects with chronic HBV infection in East Asian countries is estimated to be 0.2 per 100 person years in inactive carriers, 0.6% person-years in chronic hepatitis B (CHB) patients without cirrhosis, and 3.7% person-years in those with cirrhosis[1-3]. Therefore, it is worth focusing on antiviral therapy in patients with HBV-related HCC. This has been clarified in the recently published Chinese Expert consensus of antiviral treatment for HBV-related hepatocellular carcinoma[4]. This review provides an overview of recent studies on antiviral treatments for HBV-related HCC and emphasizes their significance.

HBV INFECTION IS AN IMPORTANT RISK FACTOR FOR HCC

Pathogenic mechanism of HBV-related HCC

In the liver of CHB patients, the immune reaction in response to persistent HBV infection may lead to long-term inflammation and injury, followed by hepatocyte regeneration, fibrogenesis and scar formation. The prolonged fibrogenic response is accompanied by regional hypoxia, angiogenesis and the distortion of tissue architecture, ultimately resulting in irreversible structural alterations in the liver and decompensated cirrhosis. During this process, HBV DNA consistently replicates and is integrated into the host genome, adding to the coexistence of metabolic disorders, inflammatory responses and oxidative injuries, which induce genetic instability and an imbalance of cell growth and apoptotic tolerance signals. These are all biologic driving forces for HCC development in CHB patients[2].

HBV DNA may integrate into host hepatocellular DNA and induce genetic alterations such as chromosomal instability, and modify host gene expression. It may also cause random genetic and chromosomal damage, chromosomal rearrangements, the activation of cellular oncogenes, and the inactivation of tumor suppressor genes, leading to dysregulation of cell growth, differentiation and apoptosis. HBV insertion, which is as frequent as 70%, may occur in genes encoding for proteins that are important in the control of cell signaling, proliferation, and viability (*e.g.*, telomerase). With repeated hepatocellular regeneration, the X, pre-S and S genes of HBV may increasingly integrate into host DNA, resulting in increased expression of intracellular HBV-encoded proteins. The viral proteins such as hepatitis B virus X protein may sensitize the host to chemical carcinogens or alter cellular oncogenes such as c-myc, and transactivate a number of cellular promoters by acting on cis-acting regulatory elements. The alteration of host gene expression associated with oncogenesis of HCC in CHB may also be mediated by epigenetic changes, which include aberrant DNA methylation, histone modifications, chromatin remodeling, transcriptional control, and the differential expression of noncoding RNAs[2,5,6].

In patients with HBV infection, the risk factors for HCC include progression to cirrhosis, longer duration of HBV infection, higher serum viral load, males with advanced age, ethnic groups native to regions of East Asia and sub-Saharan Africa, the virus genotype (genotype A in African population or genotype C in Asian population), co-infection with hepatitis C, D, or human immunodeficiency viruses, and a family history of liver cancer. Cirrhosis is the most important independent risk factor for HCC. Up to 70%-90% of primary liver cancers occur in patients with cirrhosis[1,3].

Antiviral treatment prevents the occurrence of HBV-related HCC

Effective antiviral treatment inhibits HBV replication, reduces serum viral load and accelerates hepatitis B e antigen (HBeAg) serum conversion, which may therefore alleviate liver damage and reduce the development of cirrhosis. At present, the nucleoside and nucleotide analogs (NAs) and interferon (IFN) are common clinically used antiviral drugs. NAs can be structurally grouped into (1) L-nucleosides which include lamivudine (LAM) and Telbivudine; (2) acyclicnucleotide phosphonates which include adefovir dipivoxil (ADV) and tenofovir disoproxil (TDF); and (3) D-cyclopentanes, which include Entecavir (ETV). This categorization reflects the drug's pattern of resistance. ETV and TDF are two NAs which have been recommended as first-line anti-HBV drugs by the updated consensus and recommendations on the management of CHB due to their high efficacy and high barrier to drug resistance[7-9].

The results of a meta-analysis showed that the median cumulative incidence of HCC in CHB patients treated with antiviral therapy for 3 and 5 years was lower than that without treatment (1.5% *vs* 4.0%; 5.1% *vs* 12%, respectively). Antiviral therapy significantly reduced the 3- and 5-year cumulative

incidence of HCC by 2.8% (95%CI: 0.5-5.1; *P* = 0.0162) and 7.1% (95%CI: 4.1-10.2; *P* < 0.0001), respectively[10]. Whereas in another meta-analysis which included 8 randomized controlled trials (RCTs), 8 prospective cohort studies and 19 case-control studies, the prospective cohorts and case-control series showed opposing results[11]. Although sensitivity analyses showed that antiviral therapy reduced the risk of HCC among patients with cirrhosis (RR = 0.74; 95%CI: 0.57-0.96), the strength of the evidence does not allow for extrapolation to clinical practice as the research design plays an essential role in the overall assessment.

Long-term studies on CHB patients at various stages, including asymptomatic patients, those without and with cirrhosis, showed that effective LAM and ADV treatments consistently reduced the incidence of HCC. In contrast, the development of drug resistance by HBV mutation, for example YMDD mutation due to alternations on the P region of HBV DNA and mutations on enhancer II/basal core promoter/precore (EnhII/BCP/PC), has been proven to increase HCC risk. However, it is noteworthy that on-therapy virologic remission did not completely halt the incidence of HCC, which still developed in some CHB patients within 30 mo after the start of treatment. This phenomenon was considered to be associated with the early integration of HBV into the host genome, and the patients had already developed cirrhosis, which is an independent risk factor for HCC[12].

Long-term follow-up studies of peg-IFN-α therapy showed inconsistent results. The beneficial effect was observed mainly in CHB patients with preexisting cirrhosis. Some studies also suggested that HCC incidence was lower in patients with sustained virological response (SVR) than in both non-responders and those without treatment[12]. A retrospective cohort study indicated that combination therapy with IFN-α and ribavirin significantly reduced the risk of HCC (HR = 0.76, 95%CI: 0.59-0.97), liver-related mortality (HR = 0.47, 95%CI: 0.37-0.6) and all-cause mortality (HR = 0.42, 95%CI: 0.34-0.52) in HCV-HBV dually-infected patients[13].

A retrospective review based on two prospective surveillance cohorts showed that the survival rate of patients who started antiviral therapy in the surveillance period was dramatically higher than those without any history of antiviral therapy, or those who initiated therapy after the diagnosis of HCC. The 5-year survival rates were 23.9% and 57.8%, respectively (HR = 0.472, 95%CI: 0.25-0.89, *P* = 0.0191)[14].

EFFECTS OF ANTIVIRAL TREATMENT ON THE PROGNOSIS OF HBV-RELATED HCC PATIENTS

Staging and treatment of HCC
As recommended by the guideline of the American Association for the Study of Liver Diseases (AASLD)[15], the Clinic Liver Cancer staging system classifies HCC patients into very early (single HCC $\leqslant$ 2 cm, performance status (PS) 0, Child-Pugh A, without portal hypertension), early (single HCC $\leqslant$ 5 cm or up to three nodules < 3 cm, PS 0, Child-Pugh A or B), intermediate (single or multifocal HCC > 5 cm, PS 0 to 2, Child-Pugh A or B), advanced (with symptoms and/or vascular invasion or extrahepatic spread, PS 1 to 2, Child-Pugh A or B) and end-stage (PS 3 to 4, Child-Pugh C) according to their liver function, tumor status and PS. Patients at different stages are managed by corresponding treatments.

Both surgical resection and liver transplantation (LT) are curative treatments for HCC. Other treatment options include: (1) local ablation, *e.g.*, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), microwave ablation and cryoablation; (2) transcatheter arterial chemoembolization (TACE); (3) radiation therapy, *e.g.*, three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy and stereotactic radiotherapy; (4) radio-embolization; (5) systemic chemotherapy; (6) molecularly targeted therapies; (7) traditional Chinese medicine; (8) biotherapy; and (9) symptomatic supportive treatment. Of these, PEI and RFA are highly effective and may even be curative for patients with small HCC[15-18].

HCC patients at very early and early stages should be considered for potentially curative options such as surgical resection and RFA/PEI. The early-stage patients are also recommended for LT whenever possible. A favorable prognosis can usually be achieved by these treatments. HCC patients at intermediate stages may benefit from TACE, which has been shown to induce extensive tumor necrosis in more than 50% of patients. Studies on the effects of TACE in combination with molecular-targeting agents such as sorafenib, which has been shown to inhibit tumor proliferation and angiogenesis, are underway. There is no effective therapy for HCC patients at advanced stages. Several agents have been compared to sorafenib which is unequivocally effective in improving survival. The median overall survival of sorafenib-treated patients was 10.7 mo *vs* 7.9 mo in those treated with placebo (*P* < 0.001). Patients with end-stage HCC have a poor prognosis and may only receive symptomatic supportive treatment[15-17].

The guideline on the diagnosis and treatment of primary liver cancer of China[18] indicates that surgical resection and LT are the first choice for the treatment of HCC if applicable. Local ablation may be an alternative therapy in patients with early-stage HCC, and may be used as part of palliative treatment in some situations. TACE is recommended for HCC patients who can not receive surgery. Modern precise radiotherapy provides a treatment option for local tumors that can not be excised by surgery. It is also used as a palliative treatment for distant metastasis.

Systemic treatment including molecular targeted drugs and systemic chemotherapy are used in patients with advanced HCC. Multi-disciplinary comprehensive treatment has been recommended in HCC patients, especially those at intermediate and advanced stages.

HBV reactivation is an important risk factor that impacts on the prognosis of HBV-related HCC after conventional therapy

HBV reactivation is defined as either a greater than 10-fold increase in serum HBV-DNA load when compared with the baseline level in HBV carriers, or the reappearance of hepatitis B surface antigen (HBsAg) or serum HBV-DNA level greater than 200 IU/mL in baseline HBsAg-negative patients. HBV reactivation is a frequent complication of systemic chemotherapy, especially in patients with detectable serum HBV DNA before chemotherapy, and those who have received intensive chemotherapy. Impaired host immunity is considered to allow active HBV replication to occur, since it can also occur after the use of other immunosuppressive therapies. The clinical consequences of HBV reactivation include provoking active hepatitis, thereby causing massive hepatic necrosis, liver failure, and even death[19].

A variety of metabolic and endocrine responses induced by surgery and anesthesia may result in an extensive immunosuppressive status in the immediate postoperative period. It has been reported that the incidence of HBV reactivation after liver resection is 28% in HBV infected patients. In patients with HBV-related HCC, the occurrence of HBV reactivation after partial hepatectomy may reach 19.1% within one year even in those with low preoperative viral load (HBV DNA < 2000 IU/mL). The incidence of postoperative hepatitis and mortality due to liver failure in HBV reactivated patients is significantly higher than those without HBV reactivation (76.3% *vs* 2.0%, *P* < 0.001, and 11.8% *vs* 6.4%, *P* = 0.002, respectively). The 3-year disease-free survival (DFS) and OS rates after resection were significantly lower in patients with HBV reactivation than those without reactivation (34.1% *vs* 46.0%, *P* = 0.009; and 51.6% *vs* 67.2%, *P* < 0.001, respectively)[20]. During a median follow-up period of 29.4 mo, 23.1% and 16.6% of HBV-related HCC patients with LT treatment experienced HBV relapse or HCC recurrence, respectively. It was also observed that HBV relapse was closely associated with HCC recurrence (*P* = 0.004), which led to an unfavorable OS[21].

Previous studies have indicated that anti-HBV therapies inhibit HBV replication, reduce serum HBV load, improve liver function, and render the patients more tolerant of conventional treatments for HCC. The treatments also reduce the incidence and severity of potentially life-threatening HBV reactivation. Early loss of HBV-DNA has been correlated with a better prognosis, delayed and reduced recurrence of HCC, and prolonged OS[22].

Antiviral treatments and surgery: In a study on HBV-related HCC patients with HBV-DNA level less than 2000 IU/mL, HBeAg positive, detectable preoperative HBV-DNA level, high Ishak inflammatory score, preoperative TACE, longer operating time, and blood transfusion were identified as independent risk factors for HBV reactivation after HCC surgery. Prophylactic antiviral therapy was found to be a protective factor. The rate of HBV reactivation in the preoperative HBV-DNA negative group was lower than that in the HBV-DNA positive group (16.7% *vs* 29.4%, *P* < 0.001)[20].

A two-stage longitudinal study showed that high viral load ($\geq 10^4$ copies/mL) significantly predicted unfavorable OS and relapse-free survival (RFS) after hepatectomy for HCC, whereas antiviral treatment significantly improved both types of survival. The RCTs on postoperative antiviral treatment with LAM, ADV or ETV showed that anti-viral treatment significantly decreased HCC recurrence and reduced HCC-related death (HR = 0.48; 95%CI: 0.32-0.70, and HR = 0.26; 95%CI: 0.14-0.50, respectively). Antiviral treatment also significantly decreased early recurrence (HR = 0.41; 95%CI: 0.27-0.62) and improved liver function at 6 mo after surgery when compared with the controls (*P* < 0.001). The treated patients with normalized liver function had a higher 2-year RFS rate than those without improvement (*P* = 0.003)[23].

With regard to anti-viral treatment with IFN, a recent randomized, observation-controlled, phase III trial which enrolled HBV-related HCC patients with curative resection suggested that adjuvant IFN-α-2b treatment only temporarily inhibited viral replication without a prominent effect on reducing HCC recurrence or mortality. At a median follow-up period of 63.8 mo, 57.5% of patients experienced tumor recurrence, and 31.3% were deceased. The cumulative 5-year RFS and OS rates of the intent-to-treat cohort were 44.2% and 73.9%, respectively. The median RFS of HBV-related HCC patients in the treatment group and the control group were 42.4 and 49.1 mo, respectively (*P* = 0.828)[24]. Meta-analyses also suggested that there was little evidence of benefit for adjuvant IFN therapy in reducing the recurrence rate or prolonging OS in patients with hepatitis B virus-related HCC after curative therapy. Further study is needed due to lack of stratified assessment for SVR[25,26].

Antiviral treatments and TACE: Based on a recent study of HBsAg positive HCC patients who underwent hepatectomy or TACE, HBV reactivation rates in the antiviral treatment group were 0% and 1.5%, and the rates of liver function deterioration were 2.4% and 1.5%, respectively. Whereas in the non-antiviral-treated control group, the rates of HBV reactivation were 15.7% and 17.5%, and the rates of liver function

deterioration were 4.1% and 8.1%, respectively. For TACE treatment in HBV-related HCC patients, the absence of antiviral treatment was a risk factor for HBV reactivation (OR = 0.083). The occurrence of HBV reactivation, baseline alanine aminotransferase (ALT) and alpha-fetoprotein levels were closely associated with the exacerbation of liver function after TACE (OR = 3.550, 1.031 and 2.832, respectively), indicating that antiviral treatment reduced the risk of HBV reactivation and protected the patients against liver failure, especially in patients undergoing TACE[27].

Antiviral treatments and radiotherapy: A retrospective study showed that the cumulative rate of HBV reactivation in patients who underwent 3D-CRT was significantly greater in patients without LAM therapy than in those with LAM therapy (21.8% *vs* 0%, *P* = 0.048) or the control group without any specific treatment (*e.g.*, 3D-CRT or LAM) (21.8% *vs* 2.3%, *P* = 0.047). Prophylactic antiviral therapy should be considered as 3D-CRT may induce HBV reactivation in patients with HBV-related HCC[28].

Selection of antiviral drugs for patients with HBV-related HCC

The Chinese Expert consensus of antiviral treatment for HBV-related hepatocellular carcinoma has indicated that antiviral therapy is an important secondary precaution for preventing the incidence of HBV-related HCC in CHB patients[4]. Indicators such as HBV DNA and HBsAg should be monitored in HBV-related HCC patients under comprehensive treatments for HCC, and NAs should be initiated as soon as possible if needed. The treatment should be individualized and the concrete regimen of NAs should refer to the guideline for CHB. The patients who are treated with TACE, radiotherapy or chemotherapy should be screened for HBsAg routinely. NAs should be administered before HCC treatments in those who are HBsAg positive, even if they have negative HBV DNA and a normal ALT level. The antiviral drugs should be continued for 6 mo after chemotherapy. Long-term antiviral treatment should be considered once a positive conversion of HBV DNA has occurred. For HBV DNA-negative patients who undergo surgery or ablation, clinicians must be vigilant for HBV reactivation. If HBV DNA is detectable during the monitoring period and remains positive after an interval of 2 wk, long-term antiviral treatment is recommended. Patients with detectable HBV DNA who undergo LT should start the antiviral treatments 1 to 3 mo before surgery.

In patients with decompensated cirrhosis who undergo LT, the aim of antiviral therapies is to lower the risk of HBV re-infection, and delay the deterioration of cirrhosis and its complications. A substantial improvement in liver function achieved by antiviral treatment in some patients may even result in their withdrawal from the transplantation list. Currently, the combination of NAs and Hepatitis B immune globulin (HBIG) is considered to be a standard care against HBV recurrence after LT. A systemic review showed that HBV recurrence in patients undergoing HBIG and ETV or TDF combination therapy was similar (1.5% *vs* 0%, *P* > 0.05), and was significantly lower than that in patients undergoing combination therapy with HBIG and LAM (1.0% *vs* 6.1%, *P* < 0.001). There were no significant differences between ETV/TDF monoprophylaxis after discontinuation of HBIG and the combination of HBIG plus ETV or TDF (3.9% *vs* 1.0%, *P* > 0.05), or the combination of HBIG plus LAM (3.9% *vs* 6.1%, *P* > 0.05)[29].

Long-term LAM mono-therapy has a much higher rate of viral resistance due to YMDD mutations, which are 24% at year 1, and may reach up to 70% at year 5. Therefore, close monitoring and timely rescue therapies are necessary. ETV and TDF are potent anti-HBV NAs with high barriers to drug resistance, thus are recommended worldwide as first-line mono-therapies for antiviral treatments, especially when long-term antiviral treatment is required. The cumulative HCC incidence at 5 years was 3.7% for the ETV and 13.7% for the control groups, respectively (*P* < 0.001). Cox proportional hazard regression analysis, after adjustment for the number of known HCC risk factors, showed that patients in the ETV group had a lower risk of HCC than those in the control group (HR = 0.37, 95%CI: 0.15-0.91; *P* = 0.03). Further analysis suggested that the treatment effect was greater in patients with a high risk of HCC (the risk scores were based on age, gender, cirrhosis status, levels of ALT, HBeAg, baseline HBV DNA, albumin, and bilirubin). In sub-analyses, the incidence of HCC at year 5 was lower in ETV-treated than non-rescue LAM treated cirrhosis patients (*P* = 0.043)[30].

A study of antiviral therapy naive patients with HBV-related advanced HCC has reported treatment outcomes during the follow-up period of 3, 6 and 12 mo, including virological, biochemical and serologic responses and the appearance of antiviral resistance which were similar in the LAM and ETV groups (all *P* > 0.05). The median OS in the LAM group was 9.6 mo, lower than that in the ETV group (13.6 mo), but not significantly different (*P* = 0.493). Thus, LAM might still be an option for antiviral treatment in HBV-related advanced HCC when the anticipated treatment time is short[31].

For hepatitis-B-related HCC patients with LAM resistance, a recent study suggested that the antiviral efficacy of LAM plus ADV combination therapy was comparable in HCC and non-HCC CHB patients. The virological response rates at months 12, 24, 36 and 48 were 33.3%, 58.3%, 50% and 33.3%, respectively, whereas the biochemical response rates were 55.6%, 58.3%, 70.0% and 58.3%, respectively. Therefore, LAM plus ADV combination therapy may be a rescue treatment for LAM-resistant HBV-related HCC patients[32].

CONCLUSION

Chronic infection with HBV is the main cause of HCC and is associated with an unfavorable prognosis. Many studies have demonstrated that timely initiation of antiviral treatment is not only essential for preventing the incidence of HCC in chronic hepatitis B patients, but also important for reducing HBV reactivation, improving liver function, reducing or delaying HCC recurrence, and prolonging overall survival of HBV-related HCC patients after curative and palliative therapies. ETV and TDF with high efficacy and a high barrier to drug resistance are recommended as first-line anti-HBV drugs. Close monitoring is essential during antiviral treatment and rescue therapy should be administered as soon as possible once drug resistance occurs.

ACKNOWLEDGMENTS

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