

WJG 20th Anniversary Special Issues (9): Hepatitis B virus

Hepatitis B viral load affects prognosis of hepatocellular carcinoma

Su Jong Yu, Yoon Jun Kim

Su Jong Yu, Yoon Jun Kim, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul 110-744, South Korea

Author contributions: Kim YJ designed research; and Yu SJ performed literature search and wrote the paper.

Correspondence to: Yoon Jun Kim, MD, Professor, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, South Korea. yoonyun@snu.ac.kr

Telephone: +82-2-20723081 Fax: +82-2-7436701

Received: October 27, 2013 Revised: January 20, 2014

Accepted: April 8, 2014

Published online: September 14, 2014

Abstract

Hepatocellular carcinoma (HCC) is a complex disease that is dually challenging to treat due to underlying chronic liver disease in addition to the cancer itself. The prognosis of patients with HCC is determined by intrahepatic tumor status and reserved hepatic function. Hepatitis B virus (HBV) is an established major risk factor of HCC development, and HBV viral load is being increasingly recognized as a prognostic factor in the presence of established HCC. High HBV viral load may affect the prognosis of HBV-related HCC patients in several ways. First, it is associated with more frequent recurrence of HBV-related HCC after treatment. Second, it is associated with more occurrence and severity of potentially life-threatening HBV reactivation. Last, it is associated with more worsened liver function, which limits the therapeutic options for HBV-related HCC. HBV, directly or indirectly, can induce hepatocarcinogenesis. In patients with a high HBV DNA level and subsequent active hepatitis, adhesion molecules expressed on the sinusoidal cells are up-regulated and may increase intrahepatic metastasis. HCC progression after treatment can lead to a poor prognosis by reducing number of normal functioning hepatocytes. Thus, high HBV viral load can affect the prognosis of patients

with HCC by frequent recurrence after treatment for HCC and deterioration of hepatic function associated with HCC progression. Recent meta-analysis showed that antiviral treatment reduces HCC recurrence and liver-related mortality after curative therapy of HCC. Given the strong relationship between high HBV DNA load and poor survival outcome of HCC patients due to cancer progression, it is expected that long-term antiviral therapy results in the sustained HBV suppression, control of inflammation, reduction in HCC progression, and eventually in improved overall survival.

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Key words: Hepatitis B virus; DNA; Hepatocellular carcinoma; Progression; Prognosis

Core tip: High hepatitis B virus (HBV) viral load reduces overall survival of patients with hepatocellular carcinoma (HCC) by the rapid progression of HCC after treatment and deterioration of hepatic function associated with HCC progression. The use of long-term antiviral therapy is recommended to result in the long-lasting suppression of HBV replication, reduction in HCC progression, and eventually in improved overall survival.

Yu SJ, Kim YJ. Hepatitis B viral load affects prognosis of hepatocellular carcinoma. *World J Gastroenterol* 2014; 20(34): 12039-12044 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i34/12039.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i34.12039>

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most frequent cause of tumor related death and hepatitis B virus (HBV) is associated with 70% of all HCC cases worldwide^[1,2]. The patients with HCC mostly have underlying

chronic liver disease including liver cirrhosis^[2,3]. Unlike other solid tumors, the prognosis of patients with HCC is influenced not only by intrahepatic tumor status, but also by underlying liver function.

Despite regular surveillance conducted in high risk populations, most patients with HCC are diagnosed in an advanced stage. Consequently, a minority of patients are suitable for surgical resection. However, the recurrence rates are able to be as high as 65%-80% in 5 years even for those patients who undergo surgical resection^[4], which results in a 5-year survival of about 40%^[5]. Several risk factors including tumor status such as tumor size, extent and presence of vascular invasion^[6], as well as hepatic functional parameters are reported to be related to an increased risk of HCC recurrence after surgical resection.

For advanced stage, rapid progression of HCC after transarterial chemoembolization (TACE) and following cancer progression-related hepatic functional deterioration are frequently reported^[7]. Previous prospective studies have reported TNM stage, Child-Pugh grade, and number of TACE were independent risk factors of survival of patients with HCC underwent TACE. These high rates of recurrence or progression after surgical resection or TACE are frequently associated with sub-optimal clinical outcome of HCC. However, there is no current agreement on a standard adjuvant or newer technology based therapies for HCC.

As regards viral factors, data showing that a high HBV viral load is a predictor of postoperative recurrence of HCC^[6,8] as well as another risk factor for *de novo* HCC development^[9,10] have been accumulating. Among known various risk factors for recurrent HCC after treatment, HBV viral load is the only correctable factor. This article reviewed the current evidence and role of HBV viral load on the prognosis of HCC.

HBV VIRAL LOAD AND POST-TREATMENT RECURRENCE FOR HBV-RELATED HCC

In several clinical studies on the postoperative HCC recurrence^[8,11,12] or progression of HCC after TACE^[7,13], patients with high serum HBV viral load at study entry had a considerably higher risk of HCC recurrence than those with low levels. In cases of liver transplantation, high HBV viral load (> 10⁵ copies/mL) before transplantation were reported to be associated with frequent HCC recurrence after transplantation^[14]. It is well recognized that there are two different types of HCC recurrence: early recurrence is due to intrahepatic spreading of the primary HCC and late recurrence is due to *de novo* multifocal hepatocarcinogenesis originating from the “field effect” in diseased liver^[15]. Although early recurrence may be affected by tumor-related factors, adhesion molecules expressed on the liver sinusoidal endothelial cells are up-regulated and may enhance intrahepatic metastasis in patients with a high HBV viral load and subsequent active

hepatitis^[16]. Furthermore, active viral replication of HBV may initiate hepatocarcinogenesis through a direct carcinogenic process by increasing the probability of hepatitis B viral DNA insertion in or near proto-oncogenes, tumor-suppressor genes, or regulatory elements of cellular DNA^[17,18]. Alternatively, HBV replication can indirectly induce *MDM2* and *p53* polymorphisms, and chromosomal instability, and chronic hepatic inflammation, which leads to hepatic fibrosis and hepatocarcinogenesis by triggering immune responses^[19]. Like other viruses, HBV induce endoplasmic reticulum (ER) stress. To alleviate the ER stress, unfolded protein response (UPR) including glucose-regulated protein 78 (GRP78) is up-regulated upon high HBV viral load^[20]. GRP78 pathway is one of the most important responders to disease-associated stress^[21] and might play an important role in the stepwise progression of HBV-related hepatocarcinogenesis^[22]. Recently, Zhu *et al*^[23] has reported that rs430397 polymorphism of *GRP78* gene may be a contributing factor to cirrhosis. In addition, the “G” allele of SNP rs391957 in the promoter of *GRP78* was strongly associated with increased HCC risk by permitting cells to acquire growth advantages under hepatocarcinogenesis and cis-regulated *GRP78* expression by providing an Ets-2 binding site^[24]. Ets-2 expression has been associated with hepatic cell regeneration and also with the development of HCC^[25].

HCC progression can lead to a worse prognosis by several ways. Hepatic functional reserve is reduced by recurrent HCCs due to the decreased number of normal functioning hepatocytes^[26]. In addition, recurrent HCC can cause hepatic functional deterioration through bile duct obstruction or portal vein thrombosis^[7].

EFFICACY OF ANTIVIRAL THERAPY ON POST-TREATMENT RECURRENCE FOR HBV-RELATED HCC

Despite the advances in therapeutic options including surgery, TACE, and sorafenib, currently there is no effective adjuvant therapy to prevent HCC recurrence^[27]. Well-known risk factors for HCC recurrence including tumor status (*e.g.*, tumor number, extent, Edmondson’s grade, presence of vascular invasion), AFP level, albumin level and the presence of cirrhosis; which were all irreversible factors^[28,29]. The only reversible factor is the HBV viral load and this correctable factor shed some light on the potential preventive effect of antiviral therapy in HBV-related HCC recurrence^[27]. Recent meta-analysis has shown that antiviral therapy is advantageous in reducing the risk of HCC recurrence after curative treatment for 41%^[27]. Multivariate analysis from a recent cohort study showed that recurrence free survival was significantly improved in patients receiving antiviral therapy including entecavir (OR = 0.625, 95%CI: 0.448-0.873, *P* = 0.006)^[30]. In another meta-analysis, antiviral therapy reduced both “early” and “late” HCC recurrence after surgical resection or radio-frequency ablation (RFA)^[31]. In cases of liver transplanta-

tion, lamivudine and hepatitis B immunoglobulin (HBIG) combination prophylaxis were independent predictors of HCC recurrence free survivals and showed a significantly lower mortality than those without prophylaxis^[52].

Although TACE is one of the most beneficial therapeutic options in the treatment of unresectable HCC, the issue of whether or not antiviral therapy may decrease HCC progression after TACE has yet to be answered. In a randomized prospective study, interferon- α treatment reduced recurrence and improved the survival of patients with HBV-related HCC after TACE^[53]. Even though interferon- α could reduce the HBV viral load^[54], possible antitumor efficacy of interferon- α might also relate to the prevention of HCC progression after TACE^[55]. Therefore, these findings require to be confirmed by large size randomized clinical trials with oral nucleos(t)ide analogs. High HBV viral load prior to TACE had an adverse effect on overall survival and this was related to the rapid progression of HCC after TACE, and subsequent cancer progression-related hepatic dysfunction^[7]. Further prospective studies are necessary to evaluate the applicability of long term prophylactic antiviral therapy in patients with high HBV viral load to prevent HCC progression and to improve overall survival of HCC patients treated with TACE^[7].

IMPACT OF HBV VIRAL LOAD AND ANTIVIRAL THERAPY ON THE UNDERLYING LIVER

Underlying liver function is a critical determinant of therapeutic options for HBV-related HCC and is the most important prognostic factor of the survival rate^[56-58]. In a follow-up study of 2763 HBsAg-seropositive adults in China, Chen *et al.*^[39] reported that high serum HBV viral load was associated with an increased mortality from chronic liver diseases and an increased morbidity of severe liver diseases among survivors. In a retrospective cohort study, the probability of hepatic decompensation was 15.4% at 5 years after starting antiviral therapy, which was markedly lower than the 5-year decompensation incidence of 45.4% in the untreated patients in the historical control group^[40]. In a large meta-analysis of 26 intervention studies including 3428 treated patients, histological grades were significantly associated with serum HBV viral load at study entry ($r = 0.78$; $P = 0.0001$) and at the end of treatment ($r = 0.71$; $P = 0.003$)^[41]. More importantly, improvement in histological grade was strongly associated with a decrease in serum HBV DNA loads ($r = 0.96$; $P = 0.001$)^[42]. In addition, the antiviral therapy group had a substantially greater increase in the residual liver volume per unit surface area after hepatic resection ($78.0 \pm 40.1 \text{ cm}^3/\text{m}^2$ *vs* $35.8 \pm 56.0 \text{ cm}^3/\text{m}^2$) at the sixth post-operative month^[43]. Even in patients with decompensated liver cirrhosis, antiviral therapies were proven to be effective in restoring liver function and improving survival especially if therapy is initiated early enough^[44]. In-

deed, in a Phase 2, double-blind, multicenter, randomized trial conducted at 39 sites, tenofovir and entecavir were well tolerated in these decompensated chronic hepatitis B (CHB) patients and associated with comparable improvement in Child and MELD scores at week 48: 37.5% of patients achieved a ≥ 2 point decrease in Child score and median change from baseline in MELD score was -2 ^[45].

The clinical spectrum of reactivated HBV on hepatic injury in HBV-related HCC patients varies; it may range from asymptomatic hepatitis to acute liver failure^[46,47]. A retrospective study was reported that the incidence of post-liver resection hepatitis and the exacerbation of CHB, along with a transient elevation in serum ALT, occurred within the first week after liver resection in 92% of the cases but was resolved by the second week^[48]. Notably, the degree of liver failure in terms of prothrombin time prolongation and bilirubin elevation were significantly worse for patients with exacerbation of CHB^[48]. Huang *et al.*^[49] demonstrated that HBV reactivation occurred after a partial hepatectomy, even in patients with a low preoperative HBV viral load ($< 2000 \text{ IU/mL}$), and the rate was 19.1% per year. The incidence of HBV reactivation after RFA was relatively low when compared with hepatic resection (5.6% *vs* 14.0%, $P = 0.0345$)^[50]. Although single TACE session does not significantly increase the risk of exacerbation of CHB^[51], repeated TACE can reactivate HBV replication^[52]. Although high pre-TACE HBV viral load was reported to be associated with frequent hepatitis exacerbation, most exacerbations responded well to on-demand antiviral therapy and thus, mortality was not found to be increased by hepatitis exacerbation^[7]. However, it is recommended to commence prophylactic antiviral agents before TACE to minimize the risk of HBV reactivation in the HBV-related HCC patients with detectable HBV DNA irrespective of transaminase level by international guidelines^[53-55].

HBV VIRAL LOAD AND ANTIVIRAL THERAPY AFFECT THE OVERALL SURVIVAL OF HBV-RELATED HCC

In the REVEAL-HBV study^[56], the mortality (per 100000 person-years) increased with baseline HBV viral load (in copies/mL) ranging from 9 (< 300), 48 (3.0×10^2 - 9.9×10^3), 75 (1.0×10^4 - 9.9×10^4), 143 (1.0×10^5 - 9.9×10^5), to 267 ($\geq 1 \times 10^6$) for chronic liver disease and cirrhosis; and 73, 48, 174, 692, and 816, respectively, for HCC^[42]. In multivariate Cox regression analyses of risk factors predicting progression to mortality, increasing HBV viral load was the strongest independent predictor of death from chronic liver disease and cirrhosis, and was second to cirrhosis in predicting death from HCC^[42]. In addition, in our previous study, a high HBV viral load prior to TACE had an adverse effect on overall survival ($P = 0.021$; HR = 1.725), high cancer progression-related mortality ($P = 0.014$; HR = 1.936), and hepatic failure-related mortality related to cancer progression ($P = 0.005$, HR =

3.908)^[7]. Thus, the use of prophylactic antiviral therapy in the HCC patients treated with TACE is recommended not only to prevent HBV reactivation but also to prevent HCC progression^[7].

Theoretically, adjustment in hepatic function may not only affect survival directly but also indirectly by influencing the patient's tolerance to various treatments for HCC recurrence. Antiviral therapy facilitated postoperative viral clearance, increased remnant liver volume, and augmented hepatocyte regeneration in HCC patients associated with active viral replication of HBV, which significantly enhanced the tolerance to following therapy for HCC recurrence^[57]. HBV evades the innate immune response to persist by simply not inducing it^[58]. However, antiviral treatment can overcome CD8⁺ T cell hyporesponsiveness in chronic HBV infection^[59] and may restore liver regeneration through reducing the epigenetic dysregulation of liver regeneration signals by HBx^[60]. Indeed, recent meta-analysis has shown that antiviral therapy has positive effects after the curative treatment of HBV-related HCC in terms of HCC recurrence, liver-related mortality (0% *vs* 8%; OR = 0.13, 95%CI: 0.02-0.69, *P* = 0.02) and overall survival (38% *vs* 42%; OR = 0.27, 95%CI: 0.14-0.50, *P* < 0.001)^[27].

CONCLUSION

Accumulating data have shown that a high HBV viral load has an adverse effect on overall survival, and that this is associated with the rapid progression of HCC after initial treatment, and following cancer progression-related worsening of hepatic function. Antiviral therapy may serve as a cost-effective and favorable alternative adjuvant therapy to improve the clinical outcomes of patients with HBV-related HCC. Given the strong relationship between high HBV viral load and poor survival outcome of HCC patients due to cancer progression, it is expected that long-term antiviral therapy results in the long-lasting suppression of HBV replication, control of inflammation, reduction in HCC progression, and ultimately in improved overall survival.

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P- Reviewer: Choe BH, Hashimoto N, Sotiropoulos GC, Zhu X
S- Editor: Ma YJ **L- Editor:** A **E- Editor:** Ma S





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ISSN 1007-9327



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