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ORIGINAL ARTICLE

The development of hepatocarcinoma after long-term antivirus treatment of Chinese patients with chronic hepatitis B virus infection: Incidence, long-term outcomes and predictive factors

Zhi-Qin Li[a,b], Chun-Ling Hu[a], Ping Yu[b], Xin-Yu Gu[a], Jia-Jia Zhang[a], Hua Li[a], Hong-Yu Zhang[a], Jun Lv[a], Yan-Min Liu[a], Qing-Lei Zeng[a], Jing-Ya Yan[a,*], Zu-Jiang Yu[a], Yi Zhang[a,b,c,d,e]

[a] *Department of infectious disease, The First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, Henan, China*
[b] *Biotherapy Center, The First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, Henan, China*
[c] *Department of Oncology, the First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, Henan, China*
[d] *School of Life Sciences, Zhengzhou University, 450052 Zhengzhou, Henan, China*
[e] *Key Laboratory of Clinical-Medicine, the First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, Henan, China*

Summary
Background: Patients with chronic hepatitis B virus (HBV) infection are at high risk for progressing to decompensated cirrhosis and hepatocellular carcinoma (HCC). Although long-term treatment with nucleos(t)ide analogues (NAs) benefits patients with chronic hepatitis B (CHB), many develop HCC. Therefore, the clinical outcomes of patients CHB who undergo long-term treatment with NAs remain to be identified. The aim of this study therefore was to evaluate the risk and predictors of patients with CHB who develop hepatitis B-induced HCC.

Abbreviations: HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; CHB, Chronic hepatitis B; HBsAg, Hepatitis B surface antigen; HBeAg, Hepatitis B e antigen; TB, Total bilirubin; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; ETV, Entecavir; ADV, Adefovir; LAM, Lamivdine; NAs, Nucleos(t)ide analogues.

* Corresponding author.
E-mail address: yanjingya666@163.com (J.-Y. Yan).

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Methods: We investigated 1200 patients with CHB who were treated with NAs for at least four years and evaluated the association of the variables ALT, HBsAg, HBV DNA, age and platelet count with the occurrence of HCC. We used multivariable analysis to identify independent risk factors for the development of HCC.
Results: HCC developed in 153 NA-treated patients. Serum HBV DNA levels of 18.17% (218/1200) patients were > 2000 IU/mL. The median level of liver stiffness measurement (LSM) of all patients was 8.3 ± 6.7 kPa vs. 19.8 ± 10.1 kPa in patients with HCC. Advanced age, lower platelet counts, positive HBV DNA load, lower ALB concentration and relatively advanced liver disease were associated with an increased risk of developing HCC. Further, TGF-β and IFN-γ levels were higher and lower in patients with HCC or CHB, respectively.
Conclusions: Hepato-carcinogenesis occurred more frequently in patients with a positive HBV DNA load and relatively advanced liver disease. Therefore, it is important to administer antiviral therapy to patients with CHB before they develop HBV-related cirrhosis.

Introduction

Hepatocellular carcinoma (HCC) is a major global health problem, and is the third and second-leading cause of cancer-related mortality worldwide and in China, respectively [1]. Individuals with chronic hepatitis B (CHB) infection are at 100-fold greater risk for developing HCC compared with those who are not infected [2—4]. Screening patients with CHB for HCC is necessary even after the clearance of serum hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA as well as remission of hepatitis, particularly for those with high titers of antibodies against hepatitis B core antigen [5,6]. Thus, evidence indicates that such patients remain at risk for HCC because of persistent latent HBV infection or integration of HBV DNA [7].

Antiviral therapy may reduce the risk of HCC for patients with hepatitis C-related fibrosis and cirrhosis [8,9]. In China and certain developing countries in Asia, the major risk factor for HCC is HBV infection [10]. Moreover, nucleos(t)ide analogues (NAs) that effectively treat chronic HBV infection may therefore benefit patients with HBV-related HCC [11,12]. Further, NAs can significantly reduce the risk of HBV related-HCC of patients with chronic HBV infection [13]. Therapy using NAs cannot completely eradicate HBV, and some patients may develop HCC despite undetectable levels of HBV-DNA, HBeAg seroconversion in HBeAg-positive patients, or the loss of HBsAg in HBeAg-negative patients.

The clinical characteristics of patients with HBV-related HCC are not well defined. Therefore, we investigated the clinical characteristics and outcomes of 1200 patients undergoing long-term therapy with NAs to identify factors for predicting the risk of developing HCC in patients chronically infected with HBV. Further, we aimed to develop markers to improve survival and delay recurrence of HBV-related HCC.

Material and methods

Patients

In this prospective study, the subjects were positive for HBV infection for at least 6 months and were regularly followed at the First Affiliated Hospital of Zhengzhou University from March 2012 to May 2015. The study included 1200 patients who fulfilled the inclusion criteria. The patients were chronically infected with HBV and were confirmed as HBsAg-positive for at least 6 months.

None of the patients were positive for anti-hepatitis C virus (HCV) antibodies (Abs) or anti-human immunodeficiency virus (HIV) Abs. Patients were excluded if they had nonalcoholic fatty liver disease or alcoholic liver disease. We excluded patients with HCC diagnosed before the onset of ETV or TDF therapy; patients coinfected with hepatitis D virus, HCV, or HIV; and patients who had undergone liver transplantation. Further, we excluded patients with a history of treatment with NAs or interferon, treatment with NAs < 24 weeks, < 18 years of age, diagnosis of HCC within 24 weeks after starting treatment with NAs treatment, or those with insufficient clinical data.

Liver cirrhosis can be confirmed using FibroScan measurements, specialized imaging techniques, and liver biopsy [14]. HCC can be diagnosed if the levels of α-fetoprotein are elevated as well as by characteristic imaging acquired using CT, MRI or both [15,16]. The severity of liver disease was graded according to the Child-Pugh score.

Patients were required to provide informed consent before participating in the study, which was conducted in accordance with the ethical guidelines of the 1995 Declaration of Helsinki. The independent Ethics Committees of the First Affiliated Hospital of Zhengzhou University approved the study.

Laboratory evaluation

Biochemical tests (liver and renal function, serum levels of total bilirubin [TB], ALT, albumin, blood urea nitrogen [BUN] and creatine) were performed at baseline. The HBV markers HBsAg, HBeAg, and titer of the antibody against HBeAg were measured using microparticle enzyme-linked immunosorbent assays (Dade Behring, Marburg, Germany). Serum HBV DNA was measured using the real-time polymerase chain reaction assay with a COBAS TaqMan 48 analyzer (Roche

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