CLINICAL—LIVER

Accuracy of Risk Scores for Patients With Chronic Hepatitis B Receiving Entecavir Treatment

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BACKGROUND & AIMS: Little is known about the validity of hepatocellular carcinoma (HCC) risk scores derived from treatment-naïve patients with chronic hepatitis B for patients treated with entecavir. **METHODS:** We performed a retrospective-prospective cohort study of 1531 patients with chronic hepatitis B (age, 51 ± 12 years; 1099 male; 332 with clinical cirrhosis) who were treated with entecavir 0.5 mg daily for at least 12 months at Prince of Wales Hospital in Hong Kong from December 2005 to August 2012. The patients were assessed once every 3 to 6 months for symptoms, drug history, and adherence; blood samples were collected for biochemical analyses. We validated 3 HCC risk scores (CU-HCC, GAG-HCC, and REACH-B scores) based on data collected when patients began treatment with entecavir and 2 years later. **RESULTS:** After 42 ± 13 months of follow-up, 47 patients (2.9%) developed HCC. The 5-year cumulative incidence of HCC was 4.3% (95% confidence interval [CI], 3.6%–5.0%). Older age, presence of cirrhosis, and virologic remission after 24 months or more of therapy were independently associated with HCC in the entire cohort; advanced age and hypoalbuminemia were associated with HCC in patients without cirrhosis. The area under the receiver operating characteristic curves (AUCs) for baseline CU-HCC, GAG-HCC, and REACH-B scores for HCC were 0.80 (95% CI, 0.75–0.86), 0.76 (95% CI, 0.70–0.82), and 0.71 (95% CI, 0.62–0.81), respectively; the time-dependent AUCs 1 to 4 years after patients started treatment were comparable to those at baseline. The cutoff value of the baseline CU-HCC score identified patients who would develop HCC with 93.6% sensitivity and 47.8% specificity, the baseline GAG-HCC score with 55.3% sensitivity and 78.9% specificity, and the baseline REACH-B score with 95.2% sensitivity and 16.5% specificity. Compared with patients with CU-HCC scores <5 at baseline, those with CU-HCC scores that either decreased from ≥5 to <5 or remained ≥5 had a higher risk of HCC (5-year cumulative incidences, 0% vs 3.9% and 7.3%; $P = .002$ and $P < .001$, respectively). **CONCLUSIONS: The CU-HCC, GAG-HCC, and REACH-B HCC risk scores accurately predict which patients with chronic hepatitis B treated with entecavir will develop HCC.**

Keywords: Cirrhosis; Entecavir; Hepatocellular Carcinoma; Risk Scores.

Chronic hepatitis B (CHB) is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in Asia.[1] Older age, cirrhosis, and a high level of hepatitis B virus (HBV) DNA are the most important predictors of HCC in patients with CHB.[2,3] Based on these parameters, a number of prediction scores have been developed and validated in the community and clinic settings.[4–7] In general, these scores have high negative predictive value in identifying patients at low risk for developing HCC. Application of these scores in the clinic can assist prognostication and decisions on HCC surveillance.

In the past 2 decades, the development of antiviral therapy has further modified the natural history of CHB. Antiviral therapy is effective in suppressing HBV DNA and reducing the risk of HCC.[8] New antiviral drugs such as entecavir have potent antiviral activity and low risk of drug resistance[9,10] and are currently recommended by international guidelines as first-line antiviral agents.[11–13] Entecavir is also effective in preventing disease progression and liver decompensation.[14,15] The beneficial effect of entecavir is closely linked to virologic response. Cirrhotic patients who achieve complete virologic response (undetectable HBV DNA) to entecavir have a lower risk of HCC and hepatic complications than those with detectable HBV DNA.[16] After curative treatment of HBV-related HCC, patients with undetectable HBV DNA after 24 weeks of entecavir therapy also have better survival.[17]

The potential benefit of entecavir leads to the question concerning the validity of the HCC risk scores, because all of them were derived from and validated in cohorts of treatment-naïve patients with CHB.[4–7] Obviously, antivi-

Abbreviations used in this paper: AUC, area under the receiver operating characteristic curve; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; ROC, receiver operating characteristic.

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ral therapy would significantly decrease serum HBV DNA levels and at the same time may alter other laboratory parameters by improving the necroinflammation (ie, lowering the alanine aminotransferase [ALT] level) and hepatic function (ie, increasing the albumin level and lowering the total bilirubin level). In the era of antiviral therapy, it is important to know if these HCC risk scores remain accurate and applicable in patients with CHB receiving antiviral treatment. In addition, all previous studies only calculated risk scores based on baseline parameters. The clinical significance of changes in scores during longitudinal follow-up has not been evaluated.

In this large-scale, real-life cohort study, we aimed to determine the factors associated with HCC in entecavir-treated patients with CHB. We also assessed the accuracy and applicability of HCC risk scores at baseline and during treatment with entecavir.

Patients and Methods

Study Population

This was a retrospective-prospective cohort study. We included consecutive patients with CHB who were treated with entecavir 0.5 mg daily for at least 12 months in the hepatitis clinics at Prince of Wales Hospital from December 2005 to August 2012. The purpose of this inclusion criterion was to avoid including patients with preexisting or undiagnosed HCC at the start of treatment with entecavir. Patients who were treated with entecavir before October 2009 were retrospectively identified from the HBV DNA record and recruited into the prospective follow-up study. All patients newly started on entecavir after October 2009 were also recruited into the longitudinal study in a prospective manner. All patients had positive hepatitis B surface antigen (HBsAg) for at least 6 months and a life expectancy of >1 year at recruitment. Patients with other chronic liver diseases, preexisting HCC or HCC diagnosed within the first year of treatment with entecavir, or Child class C cirrhosis, autoimmune hepatitis, coinfection with hepatitis C virus, or another serious concurrent illness (eg, alcoholism, uncontrolled diabetes, or cancer) were excluded. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients provided informed written consent.

Clinical and Laboratory Evaluation

At baseline (ie, when treatment with entecavir was started), patients underwent an evaluation that included a full medical history, physical examination, trans-abdominal ultrasonography, and measurement of complete blood cell count, prothrombin time and international normalized ratio, liver and renal biochemistries, HBsAg, hepatitis B e antigen (HBeAg) and antibody to HBeAg, and HBV DNA. HBV DNA was measured by TaqMan (Roche Diagnostics, Basel, Switzerland) real-time polymerase chain reaction assay validated against the EUROHEP standard with a linear range of detection from 20 to 2×10^8 IU/mL.[18] HBsAg was quantified by Architect HBsAg QT (Abbott Diagnostics, Lake Forest, IL), with 1:500 autodilution according to the manufacturer's instruction. The sensitivity of the Architect assay was 175 to 124,950 IU/mL. Those assays less than 175 IU/mL were repeated by undiluted detection (sensitivity from 0.05 to 250 IU/mL).[19]

The patients were followed up once every 3 to 6 months. During each visit, patients' symptoms and drug history and adherence were recorded. Liver biochemistry and α-fetoprotein level were checked at every visit. HBV DNA level was checked every 6 months, and HBsAg, HBeAg, and antibody to HBeAg levels were checked at least yearly. Maintained virologic response was defined as undetectable serum HBV DNA until the last visit.[9] Duration of virologic remission referred to the time in which serum HBV DNA remained undetectable, including the remission period during prior treatment. Ultrasonography of the abdomen was performed every 1 to 2 years for surveillance of HCC or more frequently if the α-fetoprotein level increased to >20 μg/L. Cirrhosis was defined as a shrunken small liver with a nodular surface noted on imaging of the liver and clinical features of portal hypertension (eg, ascites, splenomegaly, and varices).[4]

HCC Risk Scores

Three HCC risk scores—CU-HCC score,[4] GAG-HCC score,[7] and REACH-B score[6] (Supplementary Table 1)—were estimated at the time patients began treatment with entecavir and 2 years later. The CU-HCC score is composed of 5 parameters: age, albumin level, bilirubin level, HBV DNA level, and cirrhosis; it ranges from 0 to 44.5.[4] The GAG-HCC score comprises sex, age, HBV DNA level, and cirrhosis; it ranges widely to >100 because age (in years) is one of the components of the formula.[7] The REACH-B score consists of 5 parameters: sex, age, ALT level, HBeAg status, and HBV DNA level; it ranges from 0 to 17 and is primarily designed for patients without cirrhosis.[6]

The baseline risk scores were estimated based on the clinical and laboratory parameters at the time patients began treatment with entecavir, and the 2-year risk scores were estimated based on those parameters 2 years after starting treatment with entecavir. Based on the original studies of treatment-naïve patients, cutoff values of 5 (CU-HCC), 101 (GAG-HCC), and 8 (REACH-B) were recommended to predict the 3-year and 5-year risks of HCC.[4,6,7]

Primary Outcome

The primary outcomes of this study were the 3-year and 5-year incidence rates of HCC. The diagnosis of HCC was established based on histopathologic confirmation, detection of a positive lesion with at least 2 imaging techniques (trans-abdominal ultrasonography, triphasic computed tomography, magnetic resonance imaging, or hepatic angiography), or detection with one imaging technique coupled with an α-fetoprotein concentration >400 ng/mL.[20]

Statistical Analyses

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc, Chicago, IL) and SAS version 9.3 (SAS Institute, Cary, NC). Continuous variables are expressed as mean ± standard deviation or median (range) as appropriate. Qualitative and quantitative differences between subgroups were analyzed using χ^2 test or Fisher exact test for categorical parameters and Student t test or Mann–Whitney test for continuous parameters as appropriate. Univariate and multivariable analysis by time-dependent Cox proportional hazards regression model was performed to identify factors associated with HCC, allowing for certain covariates to have different values at different times while not being systematically related to time (see Supplementary Materials). Time-dependent variables include serum albumin, total bilirubin, and ALT levels and HBeAg. Effect sizes are