Hepatocellular carcinoma risk over time during long-term entecavir therapy for chronic hepatitis B

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Background/Aims: The risk of hepatocellular carcinoma (HCC) development among patients with chronic hepatitis B (CHB) could be reduced through long-term antiviral therapy (AVT), which was actually reimbursed in the Republic of Korea since 2007. Here, we aimed to evaluate the HCC risk during over time long-term AVT. **Methods:** From 2007 to 2014, treatment-naïve CHB patients receiving entecavir 0.5 mg as a first line antiviral were recruited from 4 academic teaching hospitals in the Republic of Korea. According to the AVT start year, patients were divided into two groups; early (E-Cohort: 2007~2012) and late (L-Cohort; 2013~2014) cohorts. The cumulative risk of HCC development between two groups was assessed using Kaplan-Meier method with a comparison by log-rank test and multivariate analysis was also performed using Cox-regression model. **Results:** Among a total of 2442 patients, the mean age was 48.8 years, with male predominance (63.3%). L-Cohort (n=1013) had the higher proportion of female gender (40.7% vs. 33.9%, p=0.001) and liver cirrhosis (34.3% vs. 27.4%, p<0.001), compared to E-Cohort (n=1429). The cumulative probabilities of HCC development at 1, 3, and 5 years among E-Cohort were 1.6%, 5.1%, and 8.6%, respectively, whereas those among L-Cohort were 1.2%, 5.3%, and 10.6%, respectively (p=0.206 by log-rank test). Multivariate analysis showed that age(adjusted hazard ratio [HR] 1.043, 95% confidence interval [CI] 1.027~1.058; p<0.001), male gender(adjusted HR 2.081, 95% CI 1.497~2.893; p<0.001), cirrhosis (adjusted HR 3.778, 95% CI 2.695~5.296; p<0.001), platelet count(adjusted HR 0.993, 95% CI 0.990~0.996; p<0.001) and hepatic decompensation (adjusted HR 1.558, 95% CI 1.070~2.270; p=0.021) were the independent predictors for HCC development. Similarly, after adjusting other potential predictors, there was no significant difference between E-Cohort and L-Cohort (adjusted HR 1.096, 95% CI 0.825~1.457; p=0.526). **Conclusions:** Regardless of the AVT start time, the risk of HCC development was maintained at the similar level since 2007 in the Republic of Korea. From the epidemiological viewpoint, other potential risk factors should be cautiously followed up in the future for more effective HCC surveillance.