Persistent Risk for Hepatocellular Carcinoma in Patients on Antiviral Treatment: Desperate Need for HBV Cure

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Commentary
During the past 20 years, with the advent of highly effective antiviral drugs for Hepatitis B Virus (HBV), we have witnessed successful viral suppression as well as the delay and prevention of progressive liver disease leading to cirrhosis and Hepatocellular Carcinoma (HCC).

In the past, reduced incidence of HCC with antiviral treatment has been well documented with lamivudine, entecavir and tenofovir [1-4].

Furthermore, prevention of recurrent HCC was observed by numerous investigators including ours following initial tumor ablation when patients received combined antiviral treatment [5-10].

Nonetheless, as reported previously, we are observing a persistent risk for HCC in patients who have maintained successful suppression of viral replication with undetectable serum HBV DNA and normal liver function, even in patients who have been on anti-HBV therapy for greater than 18 years [11]. The result of the observation is shown below (Table 1) [11].

In addition, among patients who are on antiviral therapy and post first tumor ablation, some of them continue developing new HC or recurrent HCC several years (5 yr to 10 yr) after the first HCC (personal communication). In most cases, however, continued antiviral therapy and additional tumor ablation has been successful and patients remain well on continued antiviral treatment.

These persistent risks for new and recurrent HCC among patients with successful control of
HBV are attributed to the incomplete control of HBV, namely due to the presence of cccDNA in the host’s hepatocytes.

While we are able to achieve a functional cure, a complete cure that is able to eliminate the cccDNA has not yet been possible. Therefore, even though HBV is not actively replicating, cccDNA remains in the nucleus of the hepatocytes and continues hepatocarcinogenic process including HBV and host DNA integration.

While we are grateful for the current management of HBV associated HCC, there is a desperate need for the drugs that can eradicate the virus. Due to the complexity of HBV replication, it has not been easy, potential strategies include preventing the entry of the virus by blocking the receptor of hepatocytes, preventing the replication of new HBV DNA from the pregenomic RNA (successful with currently available nucleoside/nucleotide analogues), enhancing the host innate immunity (such as small molecule agonists of toll-like receptors), developing a therapeutic vaccine engineered to activate an HBV-specific T cell immune response, and directly targeting cccDNA, in addition to other strategies.

Recent update of the development of potential HBV cure drugs was recently illustrated by Leverro et al. [11] and Block et al. [12]. The lucidly illustrated “the landscape of HBV cure efforts” by Leverro et al. (Figure 1) [12].

References


