Antiviral therapy in patients with chronic hepatitis B and hepatocellular carcinoma: post-thermal ablation. Better late than never?

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Antiviral therapy of chronic hepatitis B has been proven to be effective in slowing or halting the progression of the underlying liver disease [1]. Suppression of HBV DNA not only leads to marked improvement of necroinflammation, but also regression of hepatic fibrosis and even reversal of early cirrhosis [2]. Furthermore, the risk for development of hepatocellular carcinoma (HCC) is significantly reduced [3]. Unfortunately, once malignant transformation takes place “the dye is cast” and HCC can develop in spite of normalization of the aminotransferases and achievement of HBV DNA negativity. Therefore it is no surprise that Yoshida et al. observed recurrence of HCC post-thermal ablation of the initial cancer even though the underlying chronic hepatitis B responded favorably to lamivudine treatment [4]. No doubt the percentage of patients with long-term HBV DNA negativity would increase significantly with a superior antiviral regimen, for example, combination therapy such as adefovir plus lamivudine or tenofovir plus entecavir. More effective long-term HBV DNA suppression is likely to increase the survival rate, but probably will not significantly reduce the HCC recurrence rate. Nevertheless, long-term prospective trials with better antiviral regimens are in order. Historical control data will have to be incorporated in the study since it is probably unethical nowadays to follow patients with chronic hepatitis B post-HCC ablation without antiviral therapy.

How can we recognize the patient with chronic hepatitis B who is likely to develop HCC before malignant

transformation takes place? Gene profiling? Both genotype B and C are associated with higher risks of carcinogenesis [5]. Will treating the patients with a family history of HCC early in the course of chronic hepatitis B be cost-effective? Patients with high HBV DNA levels are at a greater risk for HCC, and those with genotype C are at the greatest risk [6, 7]. There is a reluctance to treat younger patients with high HBV DNA levels but normal aminotransferase values and mild underlying liver disease for fear of generating resistant mutations. Long-term therapy is more likely to lead to escape mutations and could later haunt the clinician if progressive liver disease evolves that is unresponsive to available antivirals. Clearly in cases of cirrhosis and HCC, liver transplantation with antiviral therapy in properly selected candidates will prevent recurrence of HCC and recurrent hepatitis B. However this is not a feasible therapy for the millions of patients who develop HCC. Radiofrequency ablation therapy provides potential curative treatment for HCC patients who are either ineligible or have no access for liver transplantation or surgical resection. Nevertheless, the residual native liver harbors HBV and malignant transformation. Hopefully with a better understanding of the pathogenesis of HCC in chronic hepatitis B, antiviral therapy can be initiated in selected patients earlier in the course of the disease prior to malignant transformation. Ultimately universal vaccination will reduce the incidence of HCC for future generations, but those already afflicted with chronic hepatitis B remain at risk for liver cancer. The challenge is when to intervene during the course of chronic hepatitis B in a specific patient with effective antiviral therapy that will prevent HCC. Equally challenging is to make cost-effective policies for treating chronic hepatitis B in large endemic populations, such as Southeast Asia, where HCC is among the most common causes of death.

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References

1. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256–63.
2. Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–17.
3. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. For the Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–31.
4. Yoshida H, Yoshida H, Goto E, Sato T, Ohki T, Masuzaki R, et al. Safety and efficacy of Lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma. *Hepatol Int* 2007;doi:[10.1007/s12072-007-9020-7](https://doi.org/10.1007/s12072-007-9020-7).
5. Tsubota A, Arase Y, Ren F, Tanaka H, Ikeda K, Kumada H. Genotype may correlate with liver carcinogenesis and tumor characteristics in cirrhotic patients infected with hepatitis B virus subtype adw. *J Med Virol* 2001;65:257–65.
6. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. For the REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73.
7. Chan HL, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004;53:1494–8.