

Antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after surgery: A comment for moving forward

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Abstract

Recurrence rate of hepatocellular carcinoma remains quite high even after surgery, and no postoperative therapies have been definitively shown to prevent hepatocellular carcinoma recurrence. A previous study showed that therapy with nucleos(t)ide analogues given to such patients after surgery significantly improved survival. However, many questions still exist about the usage of nucleos(t)ide analogues for patients with hepatocellular carcinoma after surgery.

Key words: Antiviral therapy; Hepatocellular carcinoma; Hepatitis B virus; Unanswered question

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Core tip: Some important points about the usage of nucleos(t)ide analogues for patients with hepatocellular carcinoma after surgery in clinic were pointed out.

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TO THE EDITOR

Recurrence rate of hepatocellular carcinoma (HCC) remains quite high even after curative resection or radiofrequency ablation (RFA), and no adjuvant thera-

pies have been definitively shown to prevent HCC recurrence^[1,2]. A previous study showed that therapy with nucleos(t)ide analogues (NAs) given to HCC patients after resection significantly improved survival^[3]. Whether the same holds for HCC patients after RFA was unclear until Lee *et al*^[4] reported their important findings that postoperative NA therapy significantly reduced 2-year recurrence rate. The authors supported their conclusions using multivariate analysis and propensity score matching. These results provide by far the strongest evidence that postoperative NA therapy can benefit patients with hepatitis B virus (HBV)-associated HCC. At the same time, methodological limitations in that study raise several important questions that must be addressed in future work.

Several of these limitations are acknowledged by Lee *et al*^[4] in their report. They did not take into account possible confounding effects due to differences in baseline viral load, HBeAg, liver function, or type of treatment after recurrence. In addition, their focus on recurrence rate as the most important outcome and the relatively short (2-year) follow-up prevented them from clarifying how NA therapy provided clinical benefit. NA therapy is not thought to directly affect tumor growth. Rather, it is thought to act in the short term by reducing the risk of HBV reactivation and improving liver function. Lee *et al*^[4] did not measure these outcomes in their study, making it impossible to examine how NA therapy reduced the recurrence rate. NA therapy is also thought to act in the long term by: (1) suppressing viral replication, which might reduce the risk of *de novo* HBV-related HCC development; and (2) reducing chronic inflammation in the remnant liver, thereby improving hepatic functional reserve after surgery and improving the patient's treatment options. Lee *et al*^[4] could not observe these mechanisms because they stopped follow-up at 2 years. As a result, Lee *et al*^[4] were able to measure only early recurrence, not late recurrence, which occurs at least 2 years after surgery or RFA. The 2-year cut-off also prevented the authors from measuring overall survival, a key outcome for establishing the efficacy of any treatment.

The results of Lee *et al*^[4] argue strongly for the therapeutic potential of postoperative NA therapy for patients with HBV-related HCC, but they fall short of definitively establishing the therapy as effective. To close this evidence gap, we recommend that future studies address the following questions^[5]: (1) Do all patients with HBV-related HCC benefit from postoperative NA therapy? What are the indications for NA therapy? Should these indications include preoperative liver function and viral load? We note that most patients in the study by Lee *et al*^[4] had early-stage tumors (< 3 cm) and cirrhosis. Also, all the patients in the former

randomized controlled trial were all with relatively early-stage tumors^[3]. In addition, almost all patients enrolled in previous studies had Child-Pugh A liver function^[3,4,6,7]. So, further studies should investigate the benefit of NA therapy for patients with Child-Pugh B or C liver function. Last but not least, is NA therapy valuable for those with serum HBV DNA less than 500 copies/mL? (2) Which NA drug(s) are the most effective and safest? Lamivudine is the first antiviral drug. Although it suppresses the virus quickly, the frequency of drug resistance is too high. Other NA drugs include adefovir dipivoxil, entecavir, and tenofovir; (3) When is the optimal time to initiate NA therapy, and how long should it last? Nowadays, doctors and patients increasingly attach importance to the phenomenon of HBV reactivation. Therefore, NA therapy should be started before surgery. One of the purposes of NA therapy is to prevent tumor recurrence. Less than two years of therapy may be not enough; and (4) Are there benefits and risks to adding a second NA drug or continuing monotherapy? Many studies reported that combined therapy with two or more NA drugs were suitable for chronic hepatitis B. However, it is unknown for patients with HCC after surgery.

Addressing these questions will be essential for defining the NA treatment regimens most likely to provide clinical benefit, as well as for identifying the most suitable patient populations.

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