Adjuvant antiviral therapy for the prevention of hepatocellular carcinoma recurrence after liver resection: indicated for all patients with chronic hepatitis B?

Clifford Akateh, Timothy M. Pawlik, Jordan M. Cloyd

Department of Surgery, The Ohio State University, Columbus, OH, USA

Correspondence to: Jordan M. Cloyd, MD. Assistant Professor of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center, 410 W 10th Ave, N-907 Doan Hall, Columbus, OH 43210, USA. Email: jordan.cloyd@osumc.edu.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Long Pan (Zhejiang University, Hangzhou, China).


doi: 10.21037/atm.2018.08.20

View this article at: http://dx.doi.org/10.21037/atm.2018.08.20

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide with an increasing incidence that affects all major demographic groups (1,2). Hepatitis B virus (HBV) infection is a major risk factor and leading cause of HCC development, accounting for approximately 33% of HCC cases worldwide (and up to 2/3 of cases in under-developed countries) (3,4). Although HCC often develops in a background of cirrhosis, HCC can develop in patients with chronic HBV even in the absence of cirrhosis due to active viral replication leading to hepatocarcinogenesis. While several treatment strategies exist for the management of HCC, surgical resection remains the preferred choice for patients with early disease, preserved liver function and appropriate functional status. Unfortunately, surgical resection in patients with underlying chronic HBV infection is associated with a high incidence of recurrence (5,6).

Over the last several years, there has been increasing evidence that antiviral treatment can decrease the incidence and progression of HCC among patients with chronic HBV infection (7-9). Even more promising, antiviral therapy may be critical in preventing HCC recurrence following resection or transplantation of HCC. In 2013, Yin et al. reported a randomized controlled trial (RCT) that evaluated the impact of nucleotide/nucleoside analog (NA) treatment on postoperative outcomes of patients with HBV-related HCC. Consistent with their concurrently published observational data, the authors observed a marked decrease in HCC recurrence and HCC-related deaths among patients who received postoperative antiviral therapy. Interestingly, the effect was noted among patients both with high HBV DNA levels (≥10^4 copies/mL) and low viral DNA levels (10). This study was, however, somewhat limited by the randomization methodology and imbalances between the two groups, making the conclusions less generalizable. Huang et al. later re-affirmed these findings through a relatively large single institution RCT. The investigators randomized 200 patients with chronic HBV who had undergone an R0 resection of HCC to either antiviral therapy or no treatment. All patients had good liver function with Child-Pugh class A and no previous HCC treatment or antiviral therapy. The authors reported an improvement in overall and recurrence-free survival (11). Contrary to Yin et al., the study only enrolled patients with high preoperative HBV-DNA levels (>2,000 IU/mL). As such, the impact of antiviral therapy on HCC recurrence in patients with low HBV-DNA remained unclear.

This study by Huang et al. (12) sought to answer this question. Specifically, in a recent issue of Annals of Surgery, Huang et al. reported the results of a single institution RCT evaluating the impact of postoperative antiviral therapy on HCC recurrence and survival following resection of HBV-related HCC. Following margin-negative resection, 200 patients (100 in each arm) with low (<2,000 IU/mL) preoperative HBV-DNA levels were randomized to receive the antiviral agent telbivudine daily versus no treatment.
The patients in the antiviral group had a better 5-year overall (64% vs. 44%) and recurrence-free (52% vs. 32%) survival, as well as a lower rate of HBV reactivation and a higher rate of undetectable HBV levels on follow-up. Importantly, the antiviral agent was orally administered, inexpensive, and associated with minimal toxicity. Of note, patients who developed HBV reactivation or demonstrated nonresponse to telbivudine were successfully switched to entecavir.

While the role of antiviral therapies in decreasing HCC incidence and recurrence is not a new concept, the results reported in this RCT address a very specific population (patients with low serum HBV DNA levels) in which data had been deficient. Furthermore, this study reaffirms several important aspects of the relationship between HBV and HCC carcinogenesis. First, the data confirm the potential for HBV reactivation even in patients with low preoperative serum HBV-DNA levels. For example, while greater than 70% of the patients in each group had undetectable HBV-DNA levels (<200 IU/mL), reactivation occurred in over 25% of patients who did not receive antiviral therapy. Therefore, low preoperative viral load was neither protective of reactivation nor tumor recurrence. Huang et al. (17) previously identified Hepatitis B surface antigen (HBsAg) as a distinguishing factor in HCC recurrence risk among patients with low preoperative HBV-DNA. Similar findings were reported by Sohn et al. (18), who noted that HBsAg levels ≥4,000 IU/mL were an independent risk factor of late recurrence. High HBsAg is thought to represent the integrated form of the virus, which might represent more infected hepatocytes, despite low viremia (17). While the exact mechanism of oncogenesis in chronic HBV infection is unclear, viral integration into the host, chronic inflammation and high expression of HBV protein X have been implicated (19). Theoretically, integration and host DNA disruption should be less frequent in patients with low viral counts. However, the presence of high HBsAg, despite low viral counts represents ongoing inflammation and thus increased risk of HCC carcinogenesis. Although HBsAg was not measured in the current study, HBs-Ag could be a potential mitigating factor in predicting late recurrence among patients with low HBV-DNA levels.

The study also highlights the relationship between early and late recurrence of HCC among patients with chronic hepatitis. Similar to the results of antiviral therapy among patients with high preoperative HBV-DNA levels (11), the study by Huang et al. demonstrated that antiviral therapy led to reductions in late (>2 years), but not early (<2 years) recurrences. This finding is not necessarily surprising since many investigators have postulated that early recurrence can be associated with tumor-related factors while late recurrence has been related to underlying HBV replication and the development of de novo tumors. Indeed, in the current study, early recurrence was associated with more traditional risk factors such as tumor size greater than 5 cm, lack of encapsulation, the presence of satellite nodules, and presence of portal vein thrombus, whereas late recurrence, on the other hand, was also associated with the Ishak fibrosis score and the presence of detectable HBV DNA. These subset analyses suggest that active treatment of HBV can reduce the incidence of new HCC (i.e., late recurrence) while additional oncologic-focused adjuvant strategies may be needed to reduce the incidence of early tumor recurrence.

Huang et al. should be congratulated on a well-designed RCT. While previous studies had suggested that patients with HCC and high preoperative HBV DNA levels benefited from postoperative antiviral therapy, the current study affirmed the significant benefits of antiviral therapy even among patients with low (and undetectable) preoperative HBV DNA levels. Future studies should aim to further explore the role of antiviral therapy in the prevention of HBV-related HCC, as well as investigate other adjuvant therapy strategies to reduce the incidence of early recurrence in high-risk patients undergoing liver resection. Given its ease of administration, low cost, favorable side effect profile, and significant improvements in recurrence-free and overall survival, these data add to an existing body of literature supporting the use of postoperative antiviral therapy in all patients with HBV-related HCC undergoing curative intent resection.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


Cite this article as: Akateh C, Pawlik TM, Cloyd JM. Adjuvant antiviral therapy for the prevention of hepatocellular carcinoma recurrence after liver resection: indicated for all patients with chronic hepatitis B? Ann Transl Med 2018;6(20):397. doi: 10.21037/atm.2018.08.20