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Recurrent Hepatocellular Carcinoma: It's the Virus!

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Hepatocellular carcinoma (HCC) remains a dreaded complication of chronic hepatitis B virus (HBV) infection. Surgical resection is the treatment of choice for patients with early-stage disease and preserved liver function. However, even successful surgical resection is fraught with high rates of disease recurrence limiting overall survival.¹ In those patients with curative surgical potential, optimizing medical care should be an essential component of a therapeutic strategy to maximize outcome. In this regard, antiviral therapy for HBV may play an important role.

With currently available antiviral agents, sustained suppression of HBV replication over long periods of time can be achieved in most patients with HBV infection with little concern for toxicity or emergence of resistant mutations. As a result, increasing number of patients undergoing surgery for HCC have been concomitantly treated with antiviral agents. The preponderance of observational data suggests antiviral therapy reduces recurrent HCC in this setting. An example is a recent large study from Taiwan which used their national health insurance data and compared 518 patients who received nucleoside analogs with 4,051 who did not after surgical resection for HBV-related HCC.² The use of nucleoside analog was associated with 33% reduction in HCC recurrence.

Despite a number of studies and meta-analyses evaluating the association between antiviral therapy and postresection recurrence of HCC, evidence from these observational data should be considered less than conclusive.³ Inherent in those data are selection of patients for antiviral therapy. For example, physicians and surgeons that have better expertise in the care of HBV-related complications may be more likely to use antiviral therapy, which may simply be a marker of better quality of care. Even in single center studies in which the number of decision makers may be small, the selection process by which some patients were

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given antiviral therapy whereas others weren't remains a potential source of significant biases.

In this issue of JCO, Yin et al⁴ present the results of a first randomized controlled trial evaluating the use of antiviral drugs after surgical resection for HCC. The trial randomly assigned 180 patients, of whom 163 were included in the analysis. Patients assigned to antiviral therapy experienced better 2-year overall (94% v 62%) and recurrence-free (56% v 20%) survival. These differences were maintained at four years after random assignment. Antiviral therapy was associated with better recurrence-free and overall survival when the analysis was stratified to high (10^4 copies/mL) and low serum HBV DNA concentrations. The article also included observational data in a cohort of 617 patients of whom approximately one third were given antiviral therapy. After adjusting for tumor characteristics that may influence the incidence of HCC recurrence, antiviral treatment and preoperative serum HBV DNA were found to have a significant impact on postoperative recurrence and subsequent death.

While these results, particularly those of the randomized trial, are exciting and significant, the study has limitations. Inexplicably, the randomization failed to balance important aspects of the two study arms. Patients who were assigned to no antiviral treatment had a significantly higher proportion of incomplete or no tumor encapsulation (73% v 53%), poor differentiation (81 v 62%) and increased serum alpha fetoprotein (>20 ng/mL, 72% v 57%). On the other hand, patients who were assigned to receive antiviral therapy were enriched with uninodular tumors (88% v 72%), small (<3 cm) lesions (14% v 6%), and low Barcelona Clinic Liver Cancer stage tumors (0 or A, 88% v 73%), although these differences did not reach statistical significance. These characteristics place patients in the antiviral group at a lower risk of tumor recurrence with a potential for clinical benefits associated with antiviral therapy. A subsequent post hoc multivariable analysis may not necessarily correct the inherent differences between the two arms.

As one considers the validity of the conclusion of the study and questions how antiviral therapy may reduce the incidence of HCC, it is useful to conceptually categorize HCC recurrences into two groups. The first is early recurrence, namely regrowth of micrometastases in the liver that were not detected and resected and would grow in the postoperative period. The other is late recurrence that arises as a metachronous tumor from a new area of dysplastic hepatocytes.

The benefits of antiviral therapy in reducing late recurrent HCCs is already accepted by many as there are data suggesting antiviral therapy may modulate the pro-oncogenic field defect in the liver. The strongest evidence to date is the well-publicized randomized trial by Liaw et al⁵ that compared lamivudine versus placebo in patients with advanced fibrosis or compensated cirrhosis and evidence of active viral replication. The incidence of (first) HCC in lamivudine-treated patients was reduced by 51% after approximately 3 years of study.⁵ There are many other nonrandomized studies that showed similar degree of reduction in HCC risk.⁶ The putative mechanism for this effect may include downregulation of hepatic inflammation and related nuclear signaling pathways that lead to neoplastic transformation at the cellular level and reversal of fibrosis and reduction of regenerative stimuli at the tissue

level. On the other hand, if integration of HBV DNA into the host genome plays a role in the development of HCC, antiviral therapy is unlikely to affect malignant potential of such genomic changes. One caution in interpreting and applying these data is that nearly all of the data that demonstrate antiviral benefits were derived from patients who were conventional candidates for treatment, namely those with abnormal ALT activities and active HBV replication with high serum HBV DNA, often confirmed by histological evidence of active hepatitis.

What is much less clear is whether anti-HBV therapy can reduce early recurrences. If the presumption is that most of these recurrences are regrowth of microscopic tumors that antedate the resection surgery, what effect would a nucleoside analog viral polymerase inhibitor have on malignant hepatocytes? The study by Yin et al⁴ provides conflicting data in this regard. In their observational study, there is little difference in recurrence free survival in the first postoperative year between antiviral and control groups (Fig 1⁴), whereas in the trial, the two groups differed widely and persistently from an early postoperative period. It is likely that the imbalance between the two arms in the trial that predisposed the control patients to early recurrence may explain part of the difference. However, the observation needs to be explained and replicated.

As one contemplates the practical implication of these data, there may be two types of patients to be considered separately. First, patients with active liver disease should be treated with antiviral agents regardless of their impact on HCC recurrence. These are patients with high ($>10^4$ units/mL) serum HBV DNA and abnormal ALT.⁷ Antiviral therapy should be prescribed in these patients to control hepatic inflammation, reduce the risk of postoperative hepatitis flare, and induce, in the long run, reversal of liver fibrosis. In these patients, if the use of antiviral therapy reduces HCC recurrence, it provides an added advantage, but it does not necessarily change practice. The other patient subset is those who do not meet the current treatment indication and an antiviral therapy would be used for the purpose of reducing HCC recurrence. These are patients with low level hepatitis BDNA levels, normal serum ALT values without advanced liver disease. Impressively, the data by Yin show a significant reduction in HCC recurrence in patients with lower viral loads. Again, while how much the imbalance between patient groups may have affected the data is unknown; these data do suggest a significant benefit for those patients receiving antiviral therapy. There is a theoretical basis for antiviral benefits in these patients. Low levels of HBV DNA replication are still associated with expression of HBV X protein, a viral protein which strongly promotes oncogenic signaling in hepatocytes.⁸ Perhaps, antiviral therapy reduces expression of HBV X protein to levels insufficient to promote HCC development.

Should every patient undergoing resection for HBV-induced HCC receive antiviral therapy? On the surface, the data by Yin et al⁴ seem to have conclusively answered the question in the affirmative. However, as we point out, the true answer may not be that straightforward, and we believe that there is room for additional data to answer remaining questions. Future studies should focus on patients who are not already candidates for antiviral therapy (low ALT and HBV DNA) and employ a careful design with appropriate blinding and stratification to ensure the highest quality data. In the meantime, we believe it is extremely important that these patients are managed by a multidisciplinary team of experts so that the

complex set of clinical decision making is properly conducted based on the anatomy and extent of the tumor and underlying hepatic function as well as virological and immunological status of HBV infection. Much can be learned by taking care of patients in integrated multidisciplinary teams as there will never be a trial tailored for every permutation of clinical scenarios encountered in clinical practice.

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