HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Current Status of the Use of Statins and Aspirin in the Chemoprevention of Hepatocellular Carcinoma

Yujin Hoshida, MD, PhD
Associate Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

G&H What are the main risk factors for hepatocellular carcinoma?

YH Hepatocellular carcinoma (HCC) almost exclusively develops from underlying chronic liver disease, which is characterized by progressive liver fibrosis. The main risk factor is hepatitis virus, particularly the hepatitis B and hepatitis C viruses. Other major causes are metabolic etiologies, which include excessive alcohol intake and nonalcoholic fatty liver disease.

After eliminating one of these risk factors (eg, hepatitis C virus by using the new generation of direct-acting antiviral drugs), the risk of HCC is substantially reduced. However, some patients still develop HCC in the liver even after having cleared the virus a decade or more ago. This clearly suggests that those etiologies create damage in the liver that does not completely go away. Thus, there could be a persisting abnormality in the liver even when successfully eliminating exposure to the risk factors, and it is therefore important to detect such abnormalities to identify patients still at risk of developing HCC.

G&H How and why should chemoprevention of HCC be considered?

YH We know which patients are at risk of HCC (ie, the individuals with the chronic liver diseases mentioned previously). Therefore, those are theoretically the patient populations that doctors might consider focusing their attention on to prevent cancer development. Chemoprevention for these patients is considered to be a rational approach of medical intervention. Given that such therapies would be used in patients who are still free of cancer and other symptoms likely for a long period of time, it would be ideal to use a nontoxic medicine that patients can take for years. However, it has been a challenge to make this type of therapy clinically available.

G&H What has the research to date shown about the possible chemopreventive effects of statins and aspirin on HCC?

YH A number of clinical studies, the vast majority of which have essentially been retrospective in nature, have suggested that the use of statins or aspirin may be correlated with a reduced risk of developing HCC over the course of the clinical observation. These drugs have been considered for some time as appealing potential HCC chemopreventive strategies because both are widely available, inexpensive, and generally well tolerated. However, there are several issues and challenges that need to be resolved for their clinical translation.

G&H What might be the potential mechanisms of action of these agents for reducing the risk of HCC?

YH There have been many experimental studies using animal models or cell-based systems, in which a number of mechanisms of action have been suggested. One is that statins may antagonize or inhibit the molecular signaling pathways, which are thought to worsen the cancer-promoting environment and transform normal liver cells into malignant cells by stimulating continuous proliferation and survival of the cells. Similarly, aspirin has been shown, at least in experimental models, to have a beneficial role in reducing chronic tissue inflammation, which promotes cancer initiation and progression. Recent studies using mouse models have found that aspirin can also inhibit platelets in the liver that secrete soluble factors, which can stimulate cancer-promoting molecular signaling in the liver and reduce HCC development.

A recent study suggested that the standard (325 mg) or low (<160 mg) dose of aspirin needs to be given for more than 5 years to see a statistically significant reduction in the risk of HCC.

G&H How strong are the current data supporting the use of statins or aspirin for HCC chemopreventive purposes?

YH There have been a number of clinical retrospective studies that can be synthesized for meta-analysis, and most of the studies have suggested that the risk of HCC can possibly be reduced by approximately 30% to 50%. However, there has not been enough prospective research thus far to conclude that aspirin or any type of statin definitively reduces the risk of HCC at a clinically meaningful magnitude and should, therefore, be taken for the sole purpose of chemoprevention of this disease. A major limitation of the studies that have been conducted to date is their retrospective nature, as therapeutic interventions should be tested in prospective clinical trials. However, it is not clear what the study design of such a prospective clinical trial should be because we do not know how much of the drug is needed or what duration of therapy should be used. In addition, some studies have suggested that the retrospective studies that have been published may actually be overestimating the beneficial effect of statins or aspirin. That is another reason why it is important to retest these agents in prospective clinical trials to confirm their real effect.

Recently, however, a few large, well-characterized studies with long follow-up periods have been published that reported on the possible required dose and duration needed to potentially acquire a reduction in HCC risk. This is a step forward for clinical testing of the drugs, as it offers an idea of what prospective clinical trials should look like in terms of the number of patients or the number of years of follow-up needed to validate the expected results.

G&H Could you discuss the research that has been performed on the ideal dose or length of therapy for statins and aspirin in this setting?

YH The identification of the ideal dose—the minimum required amount with which a beneficial effect (specifically, the reduction of HCC risk) could be expected while sparing the possibility of unfavorable side effects—is a priority of research. A recent study suggested that the standard (325 mg) or low (<160 mg) dose of aspirin needs to be given for more than 5 years to see a statistically significant reduction in the risk of HCC. Published studies have not observed a statistically significant increase in the incidence of adverse effects by taking aspirin. However, given that the therapy would be used in patients with chronic liver diseases, many of whom may have impaired liver function, treatment-related adverse effects should be carefully monitored during the prospective assessment of the drug in clinical trials to clarify that the required dose and treatment duration can be tolerated by the patients; these adverse effects should balance the magnitude of the observed benefit.

As for statins, a recent study suggested that the HCC-reducing effect is only observed in lipophilic statins and not in hydrophilic statins. Several experimental studies have compared the 2 types head to head and have found that lipophilic statins seem to show a better effect on cancer-promoting molecular pathways.

In addition, clinical studies have reported that patients with severe liver disease more frequently exhibit adverse events. This issue needs attention in the planning of clinical trials of statins.

G&H Could you further discuss the safety of aspirin and statins in this patient population?

YH It is important to keep in mind that the patients who would be receiving these agents for potential HCC chemoprevention have underlying liver diseases and, thus, may have severe impairment of their liver function.

Therefore, toxicity is a major concern in these patients compared to healthier individuals. The main risk of aspirin is bleeding. This is particularly an issue in patients with liver disease, as those with liver cirrhosis have, in general, inferior blood coagulation. Thus, the long-term administration of aspirin may increase the likelihood of bleeding complications and may also elevate the risk of life-threatening events in these patients.

In general, statins are well tolerated, but there is still a risk of liver toxicity by damaging hepatocytes. This is more concerning in patients with chronic liver diseases, especially cirrhosis, compared to healthier individuals because drug-metabolizing capabilities are impaired in patients with chronic liver diseases. Therefore, statin dosing should be determined more carefully than in healthier individuals.

G&H Has there been any research on whether certain patient subgroups appear to respond better to the use of statins or aspirin?

YH This is certainly an understudied area that needs more attention. This issue is a priority for the community because by knowing which patients are the best targets for each of these interventions, researchers can design the most cost-effective clinical trials by focusing on those subgroups of patients. Thus, a very large number of patients may not be needed, nor a very long follow-up period, such as 10 years, in clinical trials. I think that the focus of future research should be on working to identify an indicator or molecular biomarker to determine which patients are the best targets for each of these interventions.

It is also important to be able to obtain information on the molecular response to these potential chemopreventive agents via less-invasive methods, such as so-called liquid biopsies (ie, blood draws); this would help us identify the best target for the interventions and make prospective clinical testing possible in patients. The ultimate goals are to make sure that these interventions work in patients and to best utilize the effectiveness of these agents. I am aware of very few clinical studies currently underway incorporating such molecular biomarkers, but researchers are pushing toward this direction in clinical studies.

Dr Hoshida has no relevant conflicts of interest to disclose.

Suggested Reading

Athuluri-Divakar SK, Hoshida Y. Generic chemoprevention of hepatocellular carcinoma. *Ann N Y Acad Sci.* 2019;1440(1):23-35.

Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol.* 2018;68(3):526-549.

Fujiwara N, Singal AG, Hoshida Y. Dose and duration of aspirin use to reduce incident hepatocellular carcinoma. *Hepatology.* 2019;70(6):2216-2217.

Islam MM, Poly TN, Walther BA, Yang HC, Jack Li YC. Statin use and the risk of hepatocellular carcinoma: a meta-analysis of observational studies. *Cancers.* 2020;12(3):671.

Malehmir M, Pfister D, Gallage S, et al. Platelet GPIbα is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med.* 2019;25(4):641-655.

Simon TG, Duberg AS, Aleman S, et al. Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population. *Ann Intern Med.* 2019;171(5):318-327.

Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med.* 2020;382(11):1018-1028.