

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Exploring the Potential Chemoprophylactic Role of Carvedilol for Hepatocellular Carcinoma



Rohit Sinha, MBBS, FRCP
Consultant Gastroenterologist and Hepatologist
Gastroenterology and Hepatobiliary Diseases Unit
Sunderland Royal Hospital and The University of Edinburgh
Sunderland, United Kingdom

H&O What are the notable risk factors for hepatocellular carcinoma?

RS The main risk factor for hepatocellular carcinoma (HCC) is liver cirrhosis. A damaged liver with disrupted signaling pathways has carcinogenic potential. The causes of liver cirrhosis include nonalcoholic fatty liver disease, alcohol, hepatitis viruses, rare autoimmune liver diseases, and rare metabolic storage diseases such as alpha-1 antitrypsin deficiency. That is not to say HCC cannot develop in a noncirrhotic liver; it can, particularly in the setting of hepatitis B virus, where the virus itself can act as a carcinogen to cause HCC. However, it is rare for HCC to develop without cirrhosis.

One risk factor for HCC in a healthy liver is exposure to carcinogenic chemicals, such as vinyl chloride, which is used in plastic manufacturing. For this reason, exposure of such chemicals to workers is strictly regulated. Anabolic steroid use is also a recognized risk factor, particularly when used long term. Commonly used medicinal steroids such as prednisone or hydrocortisone do not have the same risks. Some naturally occurring toxins such as aflatoxin, which is found in fungus and can contaminate legumes, beans, rice, and wheat, are also associated with HCC.

Sex, race, and environment can also affect the risk of HCC. Men tend to have a higher propensity for developing HCC owing to a higher incidence of cirrhosis. However, some subvariants of HCC are more common in women; for example, fibrolamellar HCC is driven

by estrogen. In the United States, Asian Americans and Pacific Islanders have higher rates of HCC compared with patients who are Hispanic, Latino, Native American, Alaskan Native, or White. One of the most common environmental risk factors is smoking.

H&O What are the main carcinogenic pathways of HCC?

RS A number of carcinogenic pathways are upregulated in HCC. These include transforming growth factor (TGF)-beta/Smad, Wnt/B-catenin, Hedgehog, Notch, and epidermal growth factor signaling pathways. Angiogenic pathways such as vascular endothelial growth factor, hepatocyte growth factor, fibroblast growth factor, and platelet-derived growth factor are also upregulated. Downregulatory signaling pathways such as Janus kinase/STAT3 and hypoxia-inducible factor are suppressed in HCC.

H&O What have studies thus far found regarding the potential chemopreventive roles of different agents, including carvedilol, for HCC?

RS There have not been any randomized controlled trials; the studies that have been conducted thus far have mainly been observational. It has been found that intake of vegetables, a Mediterranean diet, whole grains, fish, poultry, certain macronutrients (eg, monounsaturated

fats), certain micronutrients (eg, vitamin E, vitamin B9, beta carotene, manganese, and potassium), and coffee in particular (especially filter coffee) are associated with a reduced risk for HCC. Large population cohort studies have demonstrated a chemoprophylactic role of statins, metformin, and aspirin, particularly in the setting of nonalcoholic fatty liver disease related to HCC. In animal models, adiponectin and troponin have demonstrated a chemoprophylactic role for HCC.

In addition, a retrospective cohort study conducted by Wijarnpreecha and colleagues highlighted the chemoprophylactic role of nonselective beta blockers. However, the study did not differentiate between carvedilol and other nonselective beta blockers. The data on the chemoprophylactic role of carvedilol are not strong, as they are derived from retrospective observations and animal models; nevertheless, they are promising.

H&O Why might carvedilol reduce the risk of HCC?

RS Preclinical and animal models by Ling and colleagues and Wu and colleagues have largely shown that carvedilol inhibits hepatic stellate cells that are related to collagen synthesis through TGF-beta and Smad pathways that are carcinogenic. Furthermore, carvedilol is postulated to cause a reduction in oxidative stress and decrease nuclear factor- κ beta activity, which is a precursor to HCC.

As discussed, cirrhosis is known to be the most common risk factor for HCC. El-Demerdash and colleagues demonstrated that carvedilol ameliorates fibrosis through pharmacokinetic and pharmacodynamic effects in a rat model. Similarly, Araújo Júnior and colleagues demonstrated reduction in fibrosis by alleviating oxidative stress and downregulation of Kupffer cells and hepatic stellate cells through the suppression of inflammatory cytokines.

H&O Has any research demonstrated that carvedilol has no effect on HCC risk?

RS A recent study by Cheng and colleagues looked at 5-year follow-up data on 32,000 patients and found that nonselective beta blockers offered no chemoprotection for HCC in high-risk patients with chronic hepatitis B. The authors did not differentiate those patients taking carvedilol. There were several limitations to this study, which may explain these conflicting results. Nevertheless, it should be emphasized that, presently, no high-quality studies have yet been conducted to prove the chemoprotective role of carvedilol.

H&O How does carvedilol differ from other nonselective beta blockers?

RS Carvedilol has anti- α -1 receptor activity in addition to nonselective beta-blocking activity. This additional action of carvedilol offers pharmacodynamic effects, particularly hypotensive effects. It is not known if these effects necessarily contribute to the potential chemoprotective role of carvedilol.

H&O What beneficial effects has carvedilol shown for managing portal hypertension?

RS The PREDESCI trial, a multicenter, double-blind, randomized, controlled study recently published in *Lancet*, concluded that nonselective beta blockers increase decompensation-free survival. There is irrefutable high-quality evidence supporting the use of nonselective beta blockers in the setting of portal hypertension. In a systematic review and meta-analysis, Sinagra and colleagues concluded that carvedilol has superior portal hypotensive effects compared with propranolol. A Cochrane review concluded that carvedilol had similar efficacy to band ligation for prevention of variceal bleeding.

Finally, retrospective studies, including one that my colleagues and I performed on patients with ascites, have observed improved survival benefiting patients on carvedilol.

H&O Is there a role for using carvedilol in patients with ascites then?

RS There is a common misconception regarding the use of nonselective beta blockers, carvedilol in particular, in patients with ascites. In 2010, Sersté and colleagues discouraged the use of nonselective beta blockers in the setting of severe ascites, highlighting their deleterious effects. Subsequent studies have discussed the concept of a physiologic window, first described by Krag and colleagues, within which patients with cirrhosis benefit from nonselective beta blockers and outside of which the patients may experience deleterious effects. More recently, nonselective beta blockers have demonstrated a prophylactic role for variceal bleeding. However, hazard ratios from the available data suggest that these agents may be associated with adverse outcomes in severe or refractory ascites. I believe that these data should be reviewed carefully and that the decision to use nonselective beta blockers should be made on a case-by-case basis (weighing the pros and cons, including the risk of variceal bleeding, the nature and degree of the ascites, and comorbidities of the patient).

H&O Are there any other safety concerns associated with using carvedilol, especially long term?

RS Studies on portal hypertension have demonstrated that a daily dose of 25 mg/day or higher in the context of liver disease is associated with adverse outcomes. There are also a number of contraindications to carvedilol. These include bradycardia or second- or third-degree heart block, sick sinus syndrome, systolic blood pressure below 85 mm Hg, fixed or reversible airway disease such as chronic obstructive pulmonary disease or asthma, floppy iris syndrome, history of cardiogenic shock, previous hypersensitivity or anaphylaxis to nonselective beta blockers in general or specifically carvedilol, untreated pheochromocytoma, severe peripheral vascular disease, Prinzmetal angina and fourth-degree heart block as per the New York Heart Association classification, and poor CYP2D6 metabolizers.

H&O What are the next steps in research regarding carvedilol and chemoprevention of HCC?

RS The next step is to perform large retrospective observation and then build a prospective, randomized controlled trial. I am not aware of any upcoming studies looking at the potential of carvedilol in HCC chemoprevention. However, there are 2 large randomized controlled trials (BOPPP and CALIBRE) currently underway in the United Kingdom that are both looking at carvedilol and primary prophylaxis of esophageal variceal bleeding. Post hoc analyses of these large studies may end up commenting on the chemoprophylactic role of carvedilol for HCC, although that is not one of the aims of these studies as far as I am aware.

H&O What data would be needed before this agent could theoretically be adopted as a potential chemopreventive strategy for HCC?

RS A large retrospective study looking at the potential of carvedilol as a chemoprophylactic or protective agent would be needed first. Animal studies have postulated some pathways. There are a number of confounders that

need to be accounted for before valid conclusions could be drawn on the agent's potential. Retrospective study data collection would also be needed on its safety and efficacy before moving on to a prospective, randomized controlled trial.

Disclosures

Dr Sinha has no relevant conflicts of interest to disclose.

Suggested Reading

Araújo Júnior RF, Garcia VB, Leitão RF, et al. Carvedilol improves inflammatory response, oxidative stress and fibrosis in the alcohol-induced liver injury in rats by regulating Kupffer cells and hepatic stellate cells. *PLoS One*. 2016;11(2):e0148868.

Cheng HY, Lin HC, Lin HL, Uang YS, Keller JJ, Wang LH. Association between nonselective beta-blocker use and hepatocellular carcinoma in patients with chronic hepatitis B without cirrhosis and decompensation. *Front Pharmacol*. 2022;12:805318.

El-Demerdash E, Abdel-Sattar SA, El-Bakly WM, Mohamed EA. Antifibrotic effects of carvedilol and impact of liver fibrosis on carvedilol pharmacokinetics in a rat model. *Eur J Drug Metab Pharmacokinet*. 2017;42(5):767-779.

Farzaneh Z, Vosough M, Agarwal T, Farzaneh M. Critical signaling pathways governing hepatocellular carcinoma behavior; small molecule-based approaches. *Cancer Cell Int*. 2021;21(1):208.

Ling L, Li G, Wang G, Meng D, Li Z, Zhang C. Carvedilol improves liver cirrhosis in rats by inhibiting hepatic stellate cell activation, proliferation, invasion and collagen synthesis. *Mol Med Rep*. 2019;20(2):1605-1612.

Sersté T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology*. 2010;52(3):1017-1022.

Sinagra E, Perricone G, D'Amico M, Tinè F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther*. 2014;39(6):557-568.

Sinha R, Lockman KA, Mallawaarachchi N, Robertson M, Plevris JN, Hayes PC. Carvedilol use is associated with improved survival in patients with liver cirrhosis and ascites. *J Hepatol*. 2017;67(1):40-46.

Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2019;393(10181):1597-1608.

Wijarnpreecha K, Li F, Xiang Y, et al. Nonselective beta-blockers are associated with a lower risk of hepatocellular carcinoma among cirrhotic patients in the United States. *Aliment Pharmacol Ther*. 2021;54(4):481-492.

Wu Y, Li Z, Wang S, Xiu A, Zhang C. Carvedilol inhibits angiotensin II-induced proliferation and contraction in hepatic stellate cells through the RhoA/Rho-kinase pathway. *BioMed Res Int*. 2019;2019:7932046.

A copy of this interview is appearing in the June 2022 issue of *Gastroenterology & Hepatology*