Published in final edited form as:
Cancer Prev Res (Phila). 2012 August ; 5(8): 989–991. doi:10.1158/1940-6207.CAPR-12-0247.

Can Propranalol Prevent Hepatocellular Carcinoma?

W. Thomas London[1] and **Katherine A. McGlynn**[2]

[1]Fox Chase Cancer Center, Philadelphia, Pennsylvania [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

Abstract

Beta-adrenergic signaling is involved in many processes that may contribute to cancer progression. In this issue of the journal (beginning on page **XX**), Nkontchou and colleagues report their retrospective observational finding that the beta-blocker propranolol was associated with a highly statistically significant reduction in the incidence of hepatocellular carcinoma in patients with advanced cirrhosis and related esophageal varices. This surprising finding requires confirmation, but the result is biologically plausible. Epidemiologic studies have linked beta-blockade with reduced rates of metastasis of other cancers and reduced cancer mortality. Laboratory studies suggest biological mechanisms for anti-cancer effects of beta-blockers.

Hepatocellular carcinoma (HCC) is the sixth most frequently occurring cancer and the third most common cause of cancer death in the world (1). About 80% of all HCCs occur in eastern Asia and sub-Saharan Africa, but the incidence of HCC is rising in the United States. The prognosis of HCC is poor; one year survival in the United States is only 50% and survival rates are even lower in developing countries (2).

Most HCCs develop in cirrhotic livers. Evidence suggests that the risk of HCC among persons with cirrhosis varies by the etiology of the underlying liver disease and by geographic location. The reported risks of HCC in persons with hepatitis B virus (HBV)-related cirrhosis are between 1% and 14% per year (3–4), similar to the risks (4%–14% per year) reported for persons with hepatitis C virus (HCV)-related cirrhosis (3–6). In contrast, the HCC risk associated with alcohol-related cirrhosis has been reported to be approximately 1% per year (7–8). Although not yet well defined, the risk associated with non-alcoholic steatohepatitis (NASH)-related cirrhosis was 2.6% per year in one study (5), suggesting that persons with NASH-related cirrhosis may have HCC risks as high as those for persons with viral hepatitis-related cirrhosis. The wide ranges of HCC risks in the literature may reflect variation by geographic location. In general, studies from Japan (3, 9) have reported notably higher risks among cirrhosis patients than have studies conducted in western countries (4–5, 10). Why this risk differential occurs is not clear, but it is consistent with the significantly higher overall rate of HCC in Japan in comparison with western countries (1).

Anti-viral therapy has been used to treat both HBV- and HCV-associated fibrosis and cirrhosis. In cases of chronic HBV infection, fibrosis and possibly cirrhosis can be reversed with anti-viral drugs resulting in a reduced risk of HCC. Prolonged treatment with

Corresponding Author: W. Thomas London, 333 Cottman Ave, Philadelphia, PA 19111; 215-728-2204; 215-214-4256; thomas.london@fccc.edu.

Disclosure of Potential Conflicts of Interest
No conflicts of interest. W. Thomas London 5/31/2012
No conflicts of interest. Katherine A. McGlynn 5/31/2012

lamivudine, the least-effective available antiviral drug, reduced the incidence of HCC by a significant 78% in a meta-analysis of 1267 HBV patients with advanced fibrosis or cirrhosis compared with 1022 similar patients not treated with lamivudine (11). Up to 75% of patients treated with lamivudine become resistant after 5 years. Newer antiviral drugs have much lower drug resistance rates and much greater suppression of HBV replication. One such drug, entecavir, caused regression of fibrosis in 88% of chronic HBV-infection patients and only 0.7% became resistant to the drug after five years (12). Nevertheless, it is still not certain that treatment of either HBV-associated compensated (without complications) or decompensated cirrhosis (with one or more complications including ascites, bleeding esophageal varices, encephalopathy, or hepato-renal syndrome) with antiviral drugs results in a reduced risk of HCC. The evidence is clearer in HCV-associated advanced fibrosis and cirrhosis, where prolonged anti-HCV therapy with interferon-α2b does not reduce the risk of HCC (13–14). It is possible that one of the new protease inhibitors, boceprevir or telaprevir, might reduce the risk of HCC in established HCV associated cirrhosis, but this has yet to be shown in randomized clinical trials. At the present time, there is no known therapy that will reduce the risk of HCC in persons with HCV-associated cirrhosis.

Therefore, the report in this issue of the journal by Nkontchou and colleagues of an association of treatment with the beta-blocker (beta-adrenergic–signaling blocker) propranolol with a reduced incidence of HCC in patients with advanced HCV-associated cirrhosis and esophageal varices is of great interest. The investigators conducted a retrospective analysis of HCC incidence in 50 of these patients who were treated with propranolol versus in 43 such patients who were not so treated. Beta-blockers have been used for many years to reduce the risk of hemorrhage from esophageal varices by reducing pressure in the portal vein and its tributaries. Portal hypertension is a severe, common complication of cirrhosis. Measurement of the hepatic venous pressure gradient (HVPG) is the best available method to evaluate the presence and severity of portal hypertension. The goal of beta-blocker treatment is to reduce HVPG to < 12 mm of mercury a level at which there is little risk of bleeding (15). Once started on beta-blocker treatment to reduce the risk of variceal hemorrhage, patients are maintained on therapy indefinitely.

In the Nkontchou et al. study, 38 of the 50 propranolol-treated patients and 34 of the 43 non–propranolol-treated patients had ligation of esophageal veins (banding). After five years of follow-up, HCC developed in 4% of the propranolol-treated patients and 20% of the non-propranolol patients. This difference was highly statistically significant by multivariate analysis [hazard ratio (HR) = 0.16; $P = 0.0005$]. This is a retrospective, observational study, and so the result could have been influenced by unknown confounders. Therefore, it would be helpful (albeit non-conclusive) if this study were repeated by use of data on similarly treated patients that are likely already available. Several centers must have many patients with HCV-associated cirrhosis and esophageal varices who were treated with either non-specific beta-blockers like propranolol and nadolol or specific beta-1–blockers like atenolol. If other, similarly designed observational studies supported Nkontchou et al.'s results, then randomized clinical trials would be warranted.

Even without supportive studies, there are other lines of evidence suggesting that beta-blockers could have a preventive or, possibly, a therapeutic role in HCC. In a recent observational study, beta-blockers were associated with reduced mortality from advanced melanoma (HR = 0.81) and reduced all-cause mortality (HR = 0.87; ref. (16). An important record-linkage study (connecting two independently collected sources of data) employing a national prescription database and the cancer registry in Ireland indicated that the non-specific beta-blocker propranolol, but not the specific beta-blocker atenolol, reduced breast cancer mortality (17).

If propranolol has an anti-tumor effect, it will be important to understand the mechanism of this action. Recent reviews of beta-adrenergic signaling and beta-blockers in cancer provide mechanistic insights into this issue (18–20) These reviews noted that inflammation, angiogenesis, stress, anoikis, apoptosis, cell motility, and activation of tumor viruses contribute to the initiation and progression of cancer and that all these processes are regulated to some degree by beta-adrenergic signaling. In experimental cancer models, activation of the sympathetic nervous system promotes metastasis of solid epithelial tumors. Beta-adrenergic receptors on tumor and stromal cells are activated by norepinephrine from sympathetic nerve fibers and by epinephrine in the circulation.

A study of neurotransmitter-driven regulation using PC-3 prostate carcinoma cells implanted in athymic BALB/c nude mice showed that lumbar lymph node metastases increased with administration of norepinephrine, whereas propranolol inhibited this effect (21). Growth of the primary tumor was not affected by either treatment. Other preclinical laboratory models suggest that beta-adrenergic receptor antagonists like propranolol are likely to inhibit the micrometastatic spread or invasion of early-stage tumors, rather than reducing the burden of large tumors or preventing the occurrence of new tumors (22).

If this hypothesis is correct, then treatment with non-specific beta-blockers like propranolol might prevent HCC in cirrhosis patients by preventing intra-hepatic micrometastases or invasion of surrounding liver parenchyma from a small localized tumor rather than actually preventing the formation of new HCCs. Furthermore, propranolol does not appear to be affected by the underlying etiology of the cirrhosis and therefore might ultimately be useful in reducing the risk of HCC in cirrhosis from any cause. Whatever the mechanism might be, the role of propranolol in cirrhosis and HCC could be a fertile field for further investigation.

References

1. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis. 2011; 15:223–243. vii–x. [PubMed: 21689610]
2. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012; 142:1264–1273. e1. [PubMed: 22537432]
3. Kato Y, Nakata K, Omagari K, et al. Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. Cancer. 1994; 74:2234–2238. [PubMed: 7922974]
4. Bialecki ES, Di Bisceglie AM. Clinical presentation and natural course of hepatocellular carcinoma. Eur J Gastroenterol Hepatol. 2005; 17:485–489. [PubMed: 15827437]
5. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010; 51:1972–1978. [PubMed: 20209604]
6. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology. 2009; 136:138–148. [PubMed: 18848939]
7. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004; 127:S87–S96. [PubMed: 15508108]
8. Miyakawa H, Izumi N, Marumo F, Sato C. Roles of alcohol, hepatitis virus infection, and gender in the development of hepatocellular carcinoma in patients with liver cirrhosis. Alcohol Clin Exp Res. 1996; 20:91A–94A.
9. Oka H, Kurioka N, Kim K, et al. Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. Hepatology. 1990; 12:680–687. [PubMed: 1698703]
10. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med. 1991; 325:675–680. [PubMed: 1651452]
11. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology. 2011; 54:91–100. [PubMed: 21503940]

12. Yokosuka O, Takaguchi K, Fujioka S, et al. Long-term use of entecavir in nucleoside-naive Japanese patients with chronic hepatitis B infection. J Hepatol. 2010; 52:791–799. [PubMed: 20409606]
13. Bruix J, Poynard T, Colombo M, et al. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Gastroenterology. 2011; 140:1990–1999. [PubMed: 21419770]
14. Di Bisceglie AM, Stoddard AM, Dienstag JL, et al. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. Hepatology. 2011; 53:1100–1108. [PubMed: 21480316]
15. Bosch J, Garcia-Tsao G. Pharmacological versus endoscopic therapy in the prevention of variceal hemorrhage: and the winner is. Hepatology. 2009; 50:674–677. [PubMed: 19714716]
16. Lemeshow S, Sorensen HT, Phillips G, et al. beta-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev. 2011; 20:2273–2279. [PubMed: 21933972]
17. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol. 2011; 29:2635–2644. [PubMed: 21632503]
18. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. Clin Cancer Res. 2012; 18:1201–1206. [PubMed: 22186256]
19. Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer Prev Res (Phila). 2011; 4:481–485. [PubMed: 21464029]
20. Melhem-Bertrandt A, Sood AK. New directions in reducing stress effects on cancer. Cancer Prev Res (Phila). 2012; 5:147–149. [PubMed: 22307563]
21. Palm D, Lang K, Niggemann B, et al. The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by beta-blockers. Int J Cancer. 2006; 118:2744–2749. [PubMed: 16381019]
22. Zhang D, Ma QY, Hu HT, Zhang M. beta2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFkappaB and AP-1. Cancer Biol Ther. 2010; 10:19–29. [PubMed: 20424515]