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Can non-selective beta-blockers prevent hepatocellular carcinoma in patients with cirrhosis?

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ABSTRACT

Hepatocellular carcinoma is the main liver-related cause of death in patients with compensated cirrhosis. The early phases are asymptomatic and the prognosis is poor, which makes prevention essential. We propose that non-selective beta-blockers decrease the incidence and growth of hepatocellular carcinoma via a reduction of the inflammatory load from the gut to the liver and inhibition of angiogenesis.

Due to their effect on the portal pressure, non-selective beta-blockers are used for prevention of esophageal variceal bleeding. Recently, non-hemodynamic effects of beta-blockers have received increasing attention. Blockage of β-adrenoceptors in the intestinal mucosa and gut lymphatic tissue together with changes in type and virulence of the intestinal microbiota lead to reduced bacterial translocation and a subsequent decrease in the portal load of pathogen-associated molecular patterns. This may reduce hepatic inflammation. Blockage of β-adrenoceptors also decrease angiogenesis by inhibition of vascular endothelial growth factors. Because gut-derived inflammation and neo-angiogenesis are important in hepatic carcinogenesis, non-selective beta-blockers can potentially reduce the development and growth of hepatocellular carcinoma.

Rodent and *in vitro* studies support the hypothesis, but clinical verification is needed. Different study designs may be considered. The feasibility of a randomized controlled trial is limited due to the necessary large number of patients and long follow-up. Observational studies carry a high risk of bias. The meta-analytic approach may be used if the incidence and mortality of hepatocellular carcinoma can be extracted from trials on variceal bleeding and if the combined sample size and follow up is sufficient.

Introduction

Hepatocellular carcinoma (HCC) is the main liver-related cause of death in patients with compensated cirrhosis [1]. Seven-hundred thousand people die annually from HCC making it the third most common cause of cancer-related death worldwide [2]. The early phases are asymptomatic and the prognosis is poor, which makes prevention essential.

Non-selective beta-blockers (NSBB) are recommended as prevention for variceal bleeding in patients with cirrhosis. A recent meta-analysis showed that NSBB decrease mortality in patients with cirrhosis beyond what can be explained by a reduced rate of gastrointestinal bleeding [3,4]. NSBB can in theory decrease the incidence of HCC, which could partly explain the findings in the meta-analysis.

NSBB exhibit hemodynamic and non-hemodynamic effects [3,5]. The main non-hemodynamic effects consist of decreased bacterial translocation (BT) and a reduced portal load of proinflammatory bacterial products [6,7]. NSBB may also reduce intrahepatic inflammation, but results of individual studies are ambiguous. The anti-angiogenic effects of NSBB are well known and used in the treatment of hemangiomas [8,9]. The preventive effect of NSBB in cancer formation and growth has been tested in clinical studies on ovarian and breast cancer with promising results [10–13].

As gut-derived inflammation and angiogenesis are important factors in liver carcinogenesis [1,14], we hypothesize that NSBB

Abbreviations: β-AR, beta-adrenoceptors; BT, bacterial translocation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; LPS, lipopolysaccharide; NSBB, non-selective beta-blockers; PAMP, pathogen-associated molecular pattern; TIPS, transjugular intrahepatic portosystemic shunt; TLR4, Toll Like Receptor 4; VEGF, vascular endothelial growth factor.

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have the potential to decrease the HCC incidence and HCC growth in patients with cirrhosis (Fig. 1).

The hypothesis

NSBB antagonize β_1- and β_2-adrenoceptors (β-ARs), which are present in a variety of tissue such as hepatic cells, gut-associated lymphatic tissue, intestinal mucosa, blood vessels, and smooth muscle cells. The β-ARs main ligands are the catecholamines norepinephrine and epinephrine, which are neurotransmitters of the sympathetic nervous system. Catecholamines exhibit pro-carcinogenic effects [15] and NSBB antagonize catecholamine driven cell migration, tumor angiogenesis, invasiveness and proliferation in gastric, breast and pancreatic cancer [12,16,17]. The result is cancer cell apoptosis and reduced growth. Patients with cirrhosis exhibit increased levels of catecholamines with increasing severity of liver disease [18]. NSBB may therefore be especially potent for the inhibition of carcinogenesis in cirrhosis.

Expression of β_2-ARs are increased on HCC cell membranes compared to healthy liver cells [19].The role of this remains unclear. It is more probable that NSBB exert anticarcinogenic effects via indirect mechanisms on extrahepatic and intrahepatic β_1- and β_2-ARs. NSBB would therefore in theory be more beneficial than selective beta-blockers.

In the following, we discuss different molecular mechanisms by which NSBB can potentially reduce HCC by preventing carcinogenesis, delaying growth and improving outcomes.

Preventing HCC by reducing gut-derived inflammation

Inflammatory processes are key drivers of malignant transformation in hepatocytes [20–22]. As BT constitutes the main inflammatory load to the cirrhotic liver, it is a potential target for HCC prevention [23]. The evidence on NSBB and HCC is indirect: NSBB decrease BT and gut-derived inflammation, which promote HCC development and growth.

Increased BT in cirrhosis is promoted by increased intestinal permeability, bacterial overgrowth, changes in gut microbiome and impaired host immunity. By blocking the effect of norepinephrine on β-ARs in the gut, NSBB have beneficial effects on the above mentioned parameters: Intestinal permeability is decreased in both hemodynamic responders and non-responders although the mechanism is still unknown [24]. Bacterial overgrowth is decreased by an acceleration of transit time and via modulation of iron acquisition [6,25]. Alterations in gut microbiome consists of reduced growth and adherence of *Eschericia coli* and other gram negative rods [25–27]. Improved immunologic barrier function includes chemotaxis and phagocytosis [28–30]. As a result of reduced BT, NSBB lower the portal concentration of the bacterial products pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) [6,24].

Whether intrahepatic β-antagonism can reduce intrahepatic inflammation is debated. Increased levels of proinflammatory cytokines activate intrahepatic β_1-ARs by norepinephrine. Adding NSBB do not modulate the result [31]. The interpretation of the results is complicated by the fact that catecholamines in the liver exert different effects depending on target cells, degree of sympathetic nervous system tone, sympathetic subtypes of α- and β-receptors, and receptor-affinity, -density and -stimulation [32–35]. The sympathetic nervous system has direct effects on hepatocytes, Kupffer cells and hepatic stellate cells increasing fibrosis. This may contribute to an intrahepatic preventive effect of NSBB on HCC [36].

In two studies on rodents [23,37], intestinal decontamination lead to reduced HCC tumor size and rate of metastasis. The effect was explained by a decrease in the portal concentration of PAMPs and concurrent downregulation of Toll Like Receptor 4 (TLR4). The same effect was seen in knock out mice without expression of TLR4. Gut-derived PAMPs and TLR4 activation lead to Kupffer- and hepatic stellate cell activation and subsequent release of the proinflammatory cytokines Tumor Necrosis Factor-α and interleukine-6 [21,31]. The proinflammatory cytokines increase HCC thermotolerance and may thereby negatively impact treatment with radiofrequency ablation [38]. Levels of LPS are correlated to HCC development, whereas restoration of gut homeostasis (by decreasing the number of gram negative rods) reduces the LPS load to the portal vein [39].

Delaying HCC growth by blocking angiogenesis

NSBB lead to regression of infantile hemangiomas through inhibitory effects on angiogenesis, one of which is downregulation of vascular endothelial growth factor (VEGF) [8,40]. The only approved therapy for advanced HCC (Sorafenib) is a multikinase inhibitor targeting pro-angiogenic factors including VEGF and NSBB could potentially exhibit similar effects, albeit less potent. In gastric cancer, NSBB reduce VEGF activity by decreasing the levels of nuclear factor-κβ [16]. There is no direct evidence indicating that NSBB reduce HCC tumor growth by decreasing angiogenesis.

How the hypothesis differs from current thinking

Currently, NSBB are used for prevention of variceal bleeding in patients with high-risk varices. It is debated whether the indication for NSBB can be expanded to other patient groups, but this debate

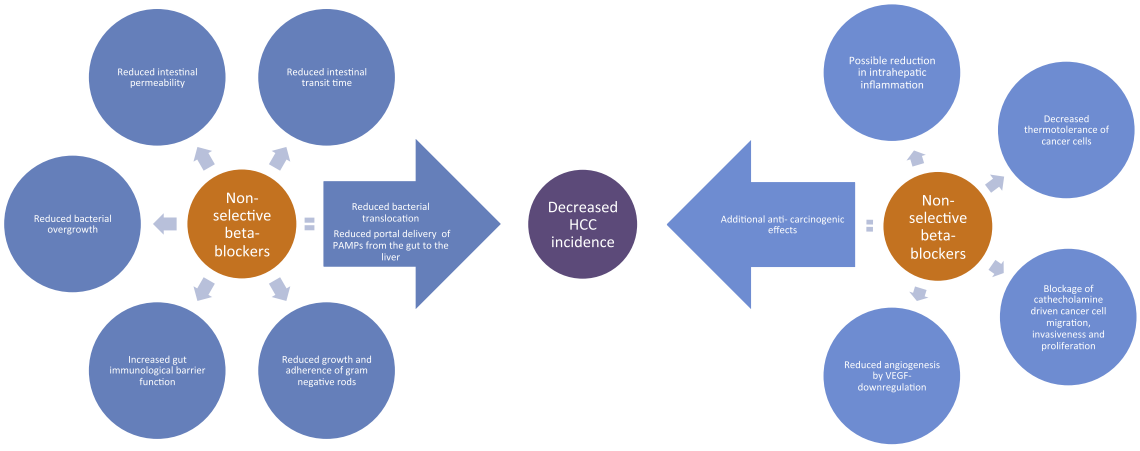

Fig. 1. Proposed pathways by which non-selective beta-blockers may decrease incidence of hepatocellular carcinoma.