Editorial

Effects of primary hypertension treatment in the oncological outcomes of hepatocellular carcinoma

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It is known that essential hypertension is associated with metabolic syndrome, which is characterized by insulin resistance and is strongly related to the development of fatty liver (1). Diabetes mellitus and hyperlipidemia increase the risk of hepatocellular carcinoma (HCC), and the use of drugs against these diseases such as metformin and statin therapy has been linked to a decrease in the risk of HCC. The primary hypertension has been associated with an increased HCC mortality but the mechanisms of this relationship are not well known. Kasmari *et al.* showed an independent risk association between hypertension and HCC in the absence of cirrhosis (2) but, the effects of high blood pressure in patients with a HCC also influence in the cirrhosis. In cirrhotic patients, arterial hypertension produces greater systemic vascular resistance that decreases peripheral vasodilation and protects against vasodilatory complications, such as hepatorenal and hepatopulmonary syndrome. Akada *et al.* described that the rates of hepatitis C virus (HCV), hypertension, and hyperlipidemia decreased with stage progression (3), and Gomez *et al.* associated mean blood pressure with ascites in patients with compensated cirrhotic HCV, such that when the mean low blood pressure is <83.32 mmHg, an increase in cirrhosis occurs (4). In HCC patients with cirrhosis and ascites, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) interact with the renin angiotensin system with risk of renal failure, hypotension, encephalopathy and hyperkalemia (5), while calcium antagonists may increase portal hypertension and liver clearance, taking special care in a patient with liver failure (6).

Within the different routes that control blood pressure, the renin-angiotensin system acts through the retention of water and electrolytes, regulation of volemia and perfusion of the juxtaglomerular apparatus. Together with its effects on blood pressure, the renin angiotensin system can affect tumor behavior by regulating and modifying its microenvironment. Angiotensin II can promote tumor progression and spread by activating adhesion molecules in the vascular endothelium, stimulation of angiogenesis, stimulation of tumor growth factors and remodeling of the parenchyma. Thus, while angiotensin II type 1 receptors have protumoral effects, angiotensin II type 2 receptors produce opposite effects (new-cancer occurrence of lung, breast, and prostate) (7-9). For this reason, the use of drugs that block the renin-angiotensin-aldosterone system has been studied in relation to its role on tumor progression in HCC. Although Ho *et al.* evaluated the chemopreventive effects of ACEIs and ARBs in a subpopulation of a patient with high-risk HCC without finding a benefit in relation to cancer outcomes (10).

It has been observed that there is a better prognosis in

patients who have been treated with ACEIs and ARBs than in those who did not receive this antihypertensive treatment. Most studies have been conducted in patients who have not received surgical treatment. A retrospective cohort study based on 5,207 patients found that the incidence of cancer was significantly lower in those patients treated with ACEIs for >3 years, without having presented differences in those patients treated with other antihypertensive drugs (11). The study by Pinter *et al.* performed on 232 patients treated with Sorafenib or other drugs that had not been previously treated with surgery or ablative techniques, showed a statistically significant increase in overall survival in those patients undergoing treatment with ACEIs or ARBs (11.9 *vs.* 6.8 months) (12). On the other hand, other authors have suggested that renin-angiotensin system inhibitors (RASIs) prolong disease free survival without increasing overall survival. In addition, there is a common characteristic of the studies developed in this line in relation to the fact that the use of RASIs can be especially useful when combined with other treatments (13).

In animal models, Arima *et al.* indicated that hypertension is a potential risk factor for liver injury and hepatic fibrosis through glucose intolerance and decreased IL-10-mediated for HO-1-induced anti-inflammatory mechanisms (14). Yoshiji *et al.* have also suggested in rats, a potential role for angiotensin II in the progression of non-alcoholic fatty liver disease to hepatic fibrosis, and the ACEI perindopril decreased tumor growth by suppressing the endothelial vascular growth factor (15). In their recent study, "*Renin-angiotensin inhibitors were associated with improving outcomes of HCC with primary hypertension after hepatectomy*", Feng *et al.* studied the results of patients with HCC with primary arterial hypertension after having undergone hepatectomy (16). They included patients with BCLC stages 0, A and B with a pathological diagnosis of HCC, with no preoperative downstaging treatment with a Child-Pugh A or B liver function. Two main groups were established, treated with RASI and those treated with another type of antihypertensive (non-RASI group). In the RASI group, the disease free survival and overall survival was statistically significant higher than in non-RASI group without finding differences between beta-blocker group *vs.* non-beta-blocker group or in CCB group *vs.* non-CCB group. Extrahepatic metastases occurred in 4 patients were in the RASI group (2.8%) and in 19 patients in the non-RASI group (7.8%). Even so, the conclusions of these studies should be interpreted with caution due to a series of limitations such as differences in population profiles, types of cancer examined, agents used and the dose and duration of administration of these agents, retrospective nature of the study, and the non-determination of cancer-specific mortality.

Drug repurposing is related to the use other than initially thought of a drug previously approved by the Food and Drug Administration (FDA). These medications are characterized because they have been tested from the point of view of efficacy, toxicity and safety, which allows their use for other purposes with the certainty that they have no adverse effects on patients (17). One of the fields where this concept had been most widely developed was oncological patients. The most studied drugs were antibiotics, proton pump inhibitors, non-steroidal anti-inflammatory drugs or antihypertensives. Currently, there are different projects on the reuse of drugs in oncology outside of its previous indication that guarantee adequate experimental evidence and good toxicity profile to be used in trials on the multidisciplinary management of cancer patients. In the case of HCC management, different experimental studies have worked with connectivity mapping, using genetics and transcriptomics as a drug repurposing method. An important line of current research described antimalarial drugs such (artemisinins, doxycycline) (18,19), commonly used drugs (statins, metformin) (20,21), others such as mebendazole or diclofenac (22) or drugs treatment based on molecular targets (dasatinib, brigatinib, Regorafenib, Sunitinib, Thalidomide, Pranlukast or Lenvatinib) (18).

In spite of the promising results found in the literature, it would be a mistake to rule RASIs indiscriminately to all patients with HCC. On the one hand, the benefit has been demonstrated in patients who presented with hypertension prior to the diagnosis of HCC, and it is not comprehensible to all patients with a recent diagnosis of the tumor that has not previously received this antihypertensive treatment. On the other hand, there are possible serious side effects of RASis in advanced cirrhosis such as hypotension or renal failure, which require the use of these drugs with caution and can lead to significant bias in the studies. Finally, the lack of consensus about treatment guidelines and the time needed to use RASIs to obtain a prognostic benefit are points that remain obscure and research in these fields can help shed light on the role of these repurposed drugs in the treatment of cancer.

In conclusion, arterial hypertension plays a fundamental role in liver damage, fibrosis and steatosis along with the rest of the metabolic syndrome diseases. The pharmacological treatment of these pathologies seems to be

related to an added beneficial effect. Current studies about drug repurposing are a promising line of research that can help improve the prognosis of cancer patients. With regard to HCC, the correct management of perioperative arterial hypertension is related to a better control of the cardiovascular effects of these patients, which results in better postoperative outcomes. Even more evidence is necessary to be able to prescribe certain drugs such as RASIs with the intention of improving their survival.

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Footnote

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