Editorial

Sorafenib and metformin: to be, or not to be, that is the question

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and ranks second among global causes of cancer-related death (1). The epidemiological and etiological landscape of the disease is facing remarkable changes, due to an increasing incidence of non-alcoholic fatty liver disease (NAFLD)-associated HCC and a concomitant decrease of virus-related cases over the last two decades in Western countries (1). High prevalence of metabolic syndrome in particular in Caucasian patients is contributing to this trend. Moreover, the growing spread of these metabolic conditions in Asian countries is likely to translate into a significant increase in NAFLD-related HCC in the future even in this geographic area (1). In this scenario, exploring the impact of diabetes and anti-diabetic medications on HCC tumorigenesis and prognosis has become of paramount importance.

The biguanide metformin represents the most frequently prescribed drug for type 2 diabetes mellitus (T2DM). Metformin has been associated with a chemopreventive effect on the incidence of HCC, as reported by several studies, including a recent large systematic review with network meta-analysis conducted on 13 studies (2,3). On the contrary, the prognostic relevance of metformin treatment in patients who have already been diagnosed with HCC remains a less explored field.

In the multi-centric retrospective study published by Schulte L. and colleagues, a significant improvement in overall survival (OS) was reported within the cohort of metformin-treated patients as part of a large overall study population of 5.093 HCC patients (4). Metformin led to a significantly longer median OS in diabetic patients, if compared both to all patients (22 *vs.* 15 months, P=0.037) and to T2DM patients not taking metformin (22 *vs.* 15 months, P=0.018). This result was confirmed even after applying a Propensity Score Match (PSM) analysis in order to reduce selection bias: patients treated with metformin still exhibited better survival outcomes (mOS 22 *vs.* 16 months, P=0.021) (4). The positive effect of metformin on survival was particularly evident in HCC patients with positive baseline prognostic features [albumin-bilirubin (ALBI) grade ≤2: 26 *vs.* 17 months, P=0.005; alpha-feto-protein (AFP) ≤200 µg/L: 31 *vs.* 18 months, P=0.004; normal C-reactive protein (CRP): 41 *vs.* 25 months, P=0.002] and in those primarily treated with potentially curative approaches, especially surgery (mOS for first-line hepatic resection or liver transplant: 32 months with metformin *vs.* 10 months, P=0.016) (4).

In line with the well-established activity of metformin in HCC risk reduction (2,3), previous retrospective studies have shown a significant decrease in recurrence rate after surgical resection, along with a significant OS improvement in HCC patients treated with metformin, compared to patients who did not take metformin (5,6). Similar results were reported in metformin-treated HCC patients receiving loco-regional therapies, such as radiotherapy and radiofrequency ablation (RFA) (7,8).

On the other hand, Schulte et al highlighted that patients treated with Sorafenib and undergoing chronic treatment with metformin had a shorter OS than patients not chronically treated with metformin (7 *vs.* 11 months, P=0.088) (4). Lack of statistical significance can be attributed to the small sample size. In addition, survival analysis applied to the subset of diabetic patients not treated with Sorafenib revealed an even more prominent advantage

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with metformin treatment (24 *vs.* 16 months; P=0.008), thus confirming the potential detrimental effect of chronic treatment with metformin in patients treated with Sorafenib (4).

The study by Schulte *et al.* validated two our study. The first evidence of a detrimental effect of metformin treatment in association with Sorafenib dates back to 2015, when our group reported decreased survival outcomes in the subset of Sorafenib-treated patients undergoing chronic treatment with metformin in a retrospective cohort of 93 HCC cases (9). In this study, the absolute difference of 2.4 months in median progression-free survival (PFS) and 4.7 months in median OS between patients taking metformin and those not taking metformin was significant (9). On the contrary, a clear, albeit not significant, advantage in terms of response, PFS and OS was observed in T2DM patients treated with insulin (9). Therefore, patients treated with Sorafenib who did not take metformin showed better survival outcomes than those reported for diabetic patients receiving both metformin and Sorafenib.

Subsequently, we aimed at validating these results in a larger case series of 279 HCC patients, consecutively treated with Sorafenib (10). In this study, metformin-treated patients showed a median PFS of 1.9 months (95% CI, 1.8–2.3) compared to 3.7 months (95% CI, 3.1–4.6) for non-diabetic patients and 8.5 months (95% CI, 5.3–11.4) for those on insulin (P<0.0001). Chronic treatment with metformin was also associated with a median OS of 6.6 months (95% CI, 4.6–8.7) compared to 10.8 months (95% CI, 9.0–13.1) for non-diabetic patients and 16.6 months (95% CI, 14.5–25.5) for the insulin group (P=0.0001) (10). Schulte and colleagues have now confirmed our findings, demonstrating a clinical negative interaction between metformin and Sorafenib in a large cohort of HCC patients (4).

Considering the proven anti-tumor effects of metformin and the higher survival associated with this drug in HCC patients (4-8), it might seem contradictory that patients undergoing chronic treatment with metformin exhibit worse survival outcomes when treated with Sorafenib. However, the molecular mechanism of action of both metformin and Sorafenib may provide an explanation for this resistance to the multikinase inhibitor by metformin-treated patients.

Metformin exerts an inhibitory activity on the proliferative mTOR pathway, both through AMPK activation and in an AMPK-independent manner (11). Through the inhibition of the mitochondrial respiratory chain complex I, metformin induces an increase in AMP, leading to AMPK activation (9,11). In addition to AMP binding, AMPK activation can be mediated by the phosphorylation by liver kinase B1 (LKB1), the calcium activated kinase (CAMKK2) or the ataxia-teleangectasia mutated (ATM) protein kinase (9,11). As a pivotal effector of the AMPK signaling cascade, the nicotinamide adenine dinucleotide $(NAD)^+$-dependent deacetylase Sirtuin-3 (SIRT-3) leads to mTOR inhibition, either directly or through hypoxia-induced factor-1α (HIF-1α) (12). The putative bridge role of SIRT-3 between metabolic diseases, metformin and HCC, has been partially confirmed by our previous study, which reported a significantly increased expression of the protein in HCC diabetic patients treated with metformin rather than insulin (10,12). In addition, SIRT-3 expression correlated with metabolic syndrome and T2DM (10). Both this AMPK-dependent and the AMPK-independent mechanisms are thought to mediate the anti-proliferative and anti-angiogenic effects of metformin in cancer.

Sorafenib inhibits VEGFR and RAF, leading to PI-3K/AKT and MAPK signaling cascades inactivation and, as a consequence, mTOR inhibition (9,10). In addition, it has also been reported that Sorafenib activates AMPK through CAMKK2 or LKB1, which results in mTOR pathway blockade (9,10,13).

Metformin and Sorafenib act on the same downstream effectors, converging on the same proliferative pathway, mTOR, which is inhibited. This might explain the resistance to Sorafenib reported in patients undergoing a chronic treatment with metformin. The underlying blockade of mTOR induced by metformin can interfere with Sorafenib, which is unable to exert its inhibitory effect on the same pathway. In addition, the chronic inhibition of mTOR pathway through metformin might induce the development of cross-resistance mechanisms towards Sorafenib.

This hypothesis does not contradict the idea that a concomitant use of metformin and Sorafenib *ab initio* in non-diabetic patients can lead to a synergistic anti-proliferative and anti-tumor effect through mTOR inhibition. In this regard, some preclinical studies demonstrated that metformin and Sorafenib cooperate to promote apoptosis and autophagy in HCC cells, exhibiting synergistic antitumor effects (14,15).

To conclude, Schulte and colleagues validated the positive prognostic role of metformin treatment in a large cohort of HCC patients, also confirming a trend towards Sorafenib resistance in patients undergoing chronic treatment with metformin. However, the similar underlying

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mechanism of action of Sorafenib and metformin, along with the preclinical evidence of a cooperation of these drugs in HCC, support the hypothesis that metformin treatment should increase Sorafenib anti-tumor activity, when started at the same time. Indeed, the absence of a previous chronic exposure to metformin would allow the concomitant and synergistic downstream activity of metformin and Sorafenib on mTOR pathway, enhancing its inhibition. Further investigations are warranted to explore the potentiality of this combination in non-diabetic HCC patients.

In conclusion, Sorafenib and metformin: to be, or not to be? We think the answer is to be, and that it is time to think of a study with Sorafenib plus metformin in patients without TDM2.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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