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Ibrutinib in Combination with Sorafenib Synergistically Inhibits Proliferation and Survival of Hepatocellular Carcinoma Cells by Targeting EGFR Signaling Pathway

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Hepatocellular carcinoma (HCC) is the second major cause of cancer-related death worldwide with limit therapeutic options. Thus, there is an urgent need to develop novel alternative therapies for HCC. In this study, we report that ibrutinib, recently approved for CLL and MCL therapies, and a covalent inhibitor of TEC (BTK, ITK etc.) and ERBB (EGFR, Her2 etc.) family of tyrosine kinases, inhibits tumorigenic functions of human and mouse HCC cells in cell culture and in HCC xenografts. More importantly, co-treatment with ibrutinib and sorafenib, an approved targeted therapy for advanced HCCs that marginally improve patients' survival, induced HCC cell apoptosis, and synergistically inhibited HCC cell proliferation including sorafenib-resistant cells. Besides, HCC spheroid formation and expression of cancer stem cell markers were suppressed by ibrutinib and sorafenib co-treatment. This combination therapy significantly suppressed the increase in tumor volume and weight of highly aggressive HCCLM3 subcutaneous xenografts in NSG mice. In addition, we show that ibrutinib inhibited ERK and Akt signaling pathways through inactivating EGFR, its irreversible substrate, and its downstream Akt and ERK signaling in HCC cells. Knocking down EGFR expression reduced sensitivity of HCC cells to ibrutinib. The constitutively active Akt signaling abrogated the synergism of two agents on inhibiting HCC cell proliferation, suggesting that Akt signaling is critical for mediating the synergistic effect of these two kinase inhibitors. Collectively, this study indicates that ibrutinib could be a re-purposed anti-HCC drug, and our data provides the evidence for the therapeutic potential of ibrutinib and sorafenib combination as an effective and attractive strategy for treating HCCs including those with sorafenib resistance.