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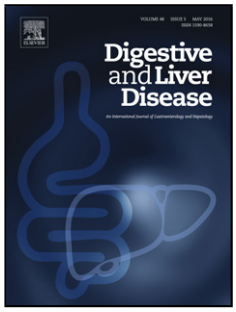

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Sorafenib and Regorafenib in HBV- or HCV- positive hepatocellular carcinoma patients: analysis of RESORCE and SHARP trials

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Dear editor,

In the RESORCE trial [1], Bruix and colleagues reported the data of regorafenib in patients with hepatocellular carcinoma (HCC) who progressed after sorafenib treatment. Regorafenib improved overall survival (OS) with an hazard ratio (HR) of 0.63 (95% CI 0.50-0.79) . In the subgroup analysis, the HR for OS in HBV-positive patients was 0.58 (95% CI 0.41-0.82 p=0.0009) with respect to 0.79 (95% CI 0.49-1.26 p=0.1583) observed in HCV-positive patients. Similar data were observed for progression free survival (0.39 vs 0.59 respectively) and time to progression (0.38 vs 0.57 respectively). Different results were observed in relation to first line treatment with sorefenib. In the subgroup analysis of the SHARP study[2], HR relative to OS was 0.76 in HBV-positive patients (95% CI 0.38-1.50 p= not significant), with respect to 0.50 (95% CI 0.32-0.77) observed in HVC-positive patients, and the data were similar for time to progression (HR 1.03 and 0.43 for HBV-positive and HCV-positive patients, respectively). Similar data were obtained in HBV positive- HCC patients by the subgroup analysis of the phase III study of Sorafenib Asia–Pacific trial, where the HR for OS was 0.74 (0.51-1.06, not significant) respect to patients with other etiology, for which the HR was 0.57 (0.29-1.33). These results seem to suggest a different efficacy of sorafenib and regorafenib in HCV or HBV – positive HCC. HCV-mediated hepatocarcinogenesis seems to be strongly mediated by type I and III IFN, which induce a plethora of IFN stimulated genes, together with the ability of HCV core to modulate intracellular pathways and cellular metabolism, through the induction of kinases phosphorylation[4]. In this setting the multikinase inhibitor sorafenib seems to be more efficacious. On the other hand, HBV-positive HCC seem to be characterized by a IL-6 dependent inflammatory process, together with different genomic perturbations due to viral DNA integration[4]. Regorafenib, an anti-VEGFR2-TIE2 and multikinase inhibitor, seems to be more efficacious in this type of HCC, in which may be there is a more

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intensive involvement of the angiogenic process. Differences in the mechanisms of action of the two drugs , together with the diversity in tumor microenvironment characteristics on the basis of HBV or HCV infection could explain the different antitumor profile.

In conclusion, these observations lead to hypothesize a different treatment strategy based on tumor etiology. Future studies should be made to evaluate if the use of first line regorafenib in HBV-positive HCC patients may be the best strategy for improving the outcome of these patients. Another interesting point that has not been taken in consideration in the subgroup analysis of both RESORCE and SHARP trials is the effect of the drugs in patients with metabolic syndrome. Specific studies aimed to understand the efficacy of drugs in relation to HCC etiology are warranted to clarify this aspect.

Authors contributions

Conception: Andrea Casadei Gardini

Manuscript writer: Andrea Casadei Gardini, Paola Ulivi.

Final approval of manuscript: Andrea Casadei Gardini, Giovanni Luca Frassineti, Francesco Giuseppe Foschi, Giorgio Ercolani, Paola Ulivi.

We declare no competing interests.

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