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Commentary

The synergistic effect of sorafenib and TNF-α inhibitor on hepatocellular carcinoma

Mingda Wang, Mengchao Wu, Tian Yang *

Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China

Hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related mortality worldwide. The global burden of HCC is increasing with an annual incidence of 1 million patients [1]. HCC treatment options vary and depend on tumor stages. Although potentially curative therapies (*e.g.*, resection, transplantation, or radiofrequency ablation) can achieve eradication of early-stage HCCs, the majority of HCC patients are diagnosed at an advanced stage, with only palliative transarterial or systemic therapies available.

In the past decade, the approval of sorafenib, a multi-target kinase inhibitor, has become a major milestone for treatment of patients with advanced-stage HCC [2]. From 2007 to 2016, sorafenib has been commonly used as the only systemic medicine for the treatment of advanced HCC. However, the therapeutic effects of sorafenib didn't achieve expectations, with minimal response rates and limited survival benefits by only extending less than 3 months of additional survival in HCC patients [3]. One possible reason for the low therapeutic efficacy is the frequently developed drug resistance, yet the underlying molecular mechanisms remain largely undetermined. This situation has prompted researchers to seek novel approaches to improve beneficial effects of sorafenib by combining with other potential agents. It is widely accepted that HCC is a highly inflammation associated tumor, which is accompanied by persistent inflammatory reaction during entire process of development [4]. Previous evidence showed that inflammation serves as a predictor of poor prognosis after sorafenib treatment in HCC patients [5]. Tumor necrosis factor (TNF)-α is one of the most important cancer-related inflammatory mediators. Relatively few studies have reported that high concentration of TNF-α can promote tumor growth, invasion, and angiogenesis *via* up-regulation of vascular endothelial growth factor (VEGF) [6], which is also a major molecular target of sorafenib. Thus, it is plausible to speculate that the TNF-α content may influence the therapeutic efficacy of sorafenib or other anti-angiogenic drugs in cancer patients. Indeed, this hypothesis is partially confirmed by a recent study that revealed a positive correlation between high expression of TNF-α and resistance to sunitinib in a renal tumor model [7]. However, the full connection of TNF-α expression to the sensitivity of HCC to sorafenib is still less investigated.

In the recent study published in *EBioMedicine*, Tan and colleagues explored the effects of TNF-α on tumor progression and examined the association of TNF-α expression and sorafenib resistance in HCC patients [8]. They reported that high expression of TNF-α was closely correlated with poor outcomes in HCC patients who received sorafenib following hepatic resection. In addition, *in vitro* experiments demonstrated that overexpression of TNF-α rendered HCC cells insensitive to sorafenib, while inhibiting TNF-α with the inhibitor Ulinastatin significantly enhanced the anti-cancer effect of sorafenib against HCC by down-regulating NF-κB/epithelial-mesenchymal transition (EMT) signaling pathway. In short, these findings indicated that overexpression of TNF-α may be responsible for sorafenib resistance, and combining sorafenib with TNF-α inhibitor may improve the effectiveness of HCC treatment, especially for patients with high expression of TNF-α.

Tan et al. showed that high expression of TNF-α promoted sorafenib resistance in HCC cells. This information may guide clinicians to predict a patient's response to sorafenib more accurately and make individualized decision on the usage of sorafenib. Mechanistically, the authors identified that the NF-κB/EMT signaling pathway was involved in the regulation of TNF-α-mediated sorafenib resistance. Since previous evidence indicated the correlation between EMT and sorafenib resistance [9], the authors further investigated the effect of sorafenib on reversing EMT with or without TNF-α. Interestingly, sorafenib could significantly suppress the EMT in HCC cells with low expression of TNF-α, but almost have no influence on EMT in those with high TNF-α content. Moreover, the inhibition of EMT by sorafenib was dramatically decreased when exogenous TNF-α was supplied, implying the critical role of TNF-α in sorafenib resistance. Subsequent experiments also showed that down-regulation of TNF-α by Ulinastatin can promote sorafenib-mediated inhibition of EMT, thus enhancing the therapeutic efficacy of sorafenib in HCC cells. This conclusion was confirmed by an *in vivo* xenograft experiment. Taken together, all these data suggest that the combined treatment with sorafenib and TNF-α inhibitor may exert a more potent therapeutic effect against HCC.

As already stated, sorafenib is only modestly effective in HCC patients. Therefore, developing better therapy is an unmet medical need. In this regard, new drugs such as lenvatinib and regorafenib have

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* Corresponding author at: Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, No. 225, Changhai Road, Shanghai 200438, China.
E-mail addresses: yangtian6666@hotmail.com, yangtianehbh@smmu.edu.cn (T. Yang).

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gradually approved by FDA for advanced HCC [10]. It is promising to extend the list of targeted drugs that applied for HCC in the future. Nevertheless, given the heavy economic burden caused by its cost, selection of suitable patients who will benefit most from sorafenib is still a major clinical issue. In general, identifying specific molecules or biomarkers that can predict the response to sorafenib in patients with advanced HCC, just as what Tan et al. have done in this study, is worthy of more concerns and supports.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

M.Wang and T. Yang wrote the manuscript. M. Wang helped with literature search. M. Wu critically revised and finalized the manuscript.

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