Commentary

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

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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...
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.

**Financial support**

This work was supported in part by the National Natural Science Foundation of China (No. 81702334, 81472284 and 81672699), and Shanghai Pujiang Program (No. 16PJ004).

**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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**References**

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30.

[2] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378–90.

[3] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25–34.

[4] Bishayee A. The role of inflammation and liver cancer. Adv Exp Med Biol 2014;816:401–35.

[5] Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol 2017;67(5):999–1008.

[6] Lewis AM, Varghese S, Xu H, Alexander HR. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. J Transl Med 2006;4:48.

[7] Mikami S, Mizuno R, Kosaka T, Saya H, Oya M, Okada Y. Expression of TNF-alpha and CD44 is implicated in poor prognosis, cancer cell invasion, metastasis and resistance to the sunitinib treatment in clear cell renal cell carcinomas. Int J Cancer 2015;136(7):1504–14.

[8] Tan W, Luo X, Li W, Zhong J, Cao J, Zhu S, et al. TNF-α is a potential therapeutic target to overcome sorafenib resistance in hepatocellular carcinoma. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2018.12.047.

[9] Mir N, Jayachandran A, Dhungel B, Shrestha R, Steel JC. Epithelial-to-mesenchymal transition: a mediator of sorafenib resistance in advanced hepatocellular carcinoma. Curr Cancer Drug Targets 2017;17(8):698–706.

[10] Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15(10):599–616.