Commentary

Comment on "combination treatment including targeted therapy for advanced hepatocellular carcinoma"

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We read with great interest the article by Lin *et al.* (1) entitled "Combination treatment including targeted therapy for advanced hepatocellular carcinoma", published in the *Oncotarget*. The authors have collected and reviewed the results of clinical trials concerning combination therapy based on molecular targeted agents (MTAs) within advanced hepatocellular carcinoma (HCC). In this article, combinative strategies include chemotherapy plus targeted therapy, diverse MTAs combination, TACE/TAE plus targeted therapy as well other combinative treatments. According to the summarized results from this paper, while various combinative treatments have been explored in clinical practice, few satisfied therapeutic effects obtained in the management of advanced HCC.

As is well-known that liver cancer, especially HCC, is the second most mortal cancer type (2), HCC is one of the most aggressive malignancies. Over half of patients with HCC present an advanced disease at diagnosis despite the major risk factors for HCC have been recognized, including hepatitis B and C, nonalcoholic fatty liver disease and alcohol-induced cirrhosis (3). For patients with advanced HCC, treatment options are limited since it is contraindication of hepatectomy or liver transplant on the basis of Milan criterion (4). In the era of targeted therapy and precision medicine, management of cancer patients in advanced stage became more promising. MTAs applied in advanced tumor (such as lung cancer and breast cancer) patients have improved the prognosis prominently (5,6). In 2008 the approval of sorafenib by FDA until then desolated scenario of advanced HCC therapy radically changed the therapeutic approach, unfolding the era of molecular targeted therapy in liver cancer.

Sorafenib, a multi-kinase inhibitor, suppressing tumor neo-angiogenesis and proliferation. It inhibits the tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2 and 3 and of the platelet-derived growth factor receptor. It also inhibits the serine-threonine kinases Raf-1 and B-Raf (7). Two large randomized controlled trials (SHARP and Asia-Pacific studies) have demonstrated that sorafenib possesses an improvement in overall survival of nearly 3 months between the sorafenib and placebo arms (10.7 *vs.* 7.9 months; 6.5 *vs.* 4.2 months, respectively) (8,9). Although many clinical trials used diverse MTAs in the therapy of HCC, both in first-line or second-line treatments, none of these agents showed preferable outcomes compared sorafenib until now (10). Therefore, the landscape of molecular-targeted therapy in advanced HCC is depressing.

Obviously, a mere 3 months overall survival prolonged by sorafenib unable to meet the requirements of the treatment of patients with advanced HCC. Form Lin's article, we know that sorafenib combined with classic chemotherapy, TACE, radiofrequency ablation (RFA) or other MTAs was inferior to sorafenib single agent in almost all clinical trials. Besides, for the lack of controlled arm setting in some trials, it's difficult to judge whether preferable outcomes would be obtained by combination therapy. It is noted that the enter criteria of most existing clinical trials were deficient in precise selection, such as specific mutation, predictive biomarkers or particular pathological pattern. This factor may induce the bad outcomes of combination treatment of targeted therapy in advanced HCC. On account of heterogeneity of HCC, featured population should be selected to accept proper combinative targeted therapy may

improve the prognosis of advanced HCC. Although it is not clear whether patients with specific genomic mutation will acquire better efficacy in comparison with patients without given mutation in the therapy of sorafenib, orderly monitor is necessary when targeted therapy is ongoing. It is advised to utilize many auxiliary means to select therapeutic method and modify patients' treatment, such as biopsy/rebiopsy, tumor genome sequence, circulating tumor DNA and so forth. In addition to improved treatment modalities, HCC surveillances in at-risk populations are critically important.

Till now, no additional molecules have yet been added to our pharmaceutical devices except sorafenib in the treatment of advanced HCC. Since sorafenib launched in 2008, numerous researchers focused on exploring its resistance mechanism, predictive biomarkers and other complementary molecular drugs to enhance its efficacy. In the past few years some breakthrough step has been the approval of sorafenib as a systemic therapy for advanced HCC. Rudalska *et al.* found elevated Mapk14-Atf2 signaling was a poor response predictor to sorafenib therapy in human HCC, and silencing Mapk14 was able to revert sorafenib resistance of p-Mapk14-expressing HCC cells (11). Wu *et al.* demonstrated ADRB2 signaling inhibited autophagic degradation of HIF1α to promote HCC progression and sorafenib resistance (12). Zhou *et al.* proved tumor-associated neutrophils recruit macrophages and T-regulatory cells can promote resistance to sorafenib in HCC, which illustrated immune system also played a crucial role in the response to sorafenib (13). Although lots of drug mechanisms have been uncovered in preclinical studies, it will take a long time to transform these achievements to clinical employment.

Targeted therapy counter to drive mutation of tumor can achieve remarkable curative effect in a short time, which may relieve patient from cancer pain and improve their quality of life (QOL). However, according to clinical practices in many kind of cancer, the efficacy brought by targeted agents is just a flash in the pan. For this characteristic of MTAs, sorafenib has been applied in the patients with large-tumor advanced HCC, hoping that dramatic shrink would be presented in tumor size so that it may offer an opportunity to process surgical resection. Curtit *et al.* reported a case that demonstrated the potential benefit gained from pre-surgery targeted therapy (14). A 56-year-old man with advanced HCC in the context of a long history of hepatitis C-related cirrhosis showed obvious tumor suppression after 6 months of sorafenib treatment. Tumor regression made surgical liver resection became possible and the pathologic examination of excision indicated that complete histologic response was achieved. In addition, targeted therapy also prolonged survival time in the advanced cancer patients with metastasis. Nakano *et al.* reported a case that a HCC patient with bone, lymph node and peritoneum metastases obtained complete response to short-term sorafenib treatment alone (15). Although these individual cases are infrequent, these hint us to a more personalized approach to medicine and of genomic investigations of tumors should be explored. The mechanisms involved in complete response that results from treatment with sorafenib are unclear, deeper understanding of the mechanisms of tumor occurrence, progression, development, and metastasis will facilitate rational utilization of sorafenib in the treatment of advanced HCC.

In general, targeted therapy in advanced HCC is still in its infancy. More effective molecular agents targeted vital pathway or genes of HCC will be came out. For patients with advanced HCC who lost surgical tumor resection or liver transplant, it is till to recommend to proceed with sorafenib treatment so far. For the exact target of sorafenib is obscure, additional work is required to clarify the molecular pathogenesis of HCC and identify key targets for therapeutic intervention. As for the combination treatment, it is meaningful to combine local treatment or palliative treatment with targeted therapy despite there is not yet an effective therapeutic approach to control and cure advanced HCC in humans.

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Footnote

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

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References

1. Lin J, Wu L, Bai X, et al. Combination treatment including targeted therapy for advanced hepatocellular carcinoma. Oncotarget 2016. [Epub ahead of print].
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015.

CA Cancer J Clin 2015;65:5-29.
3. Ronot M, Bouattour M, Wassermann J, et al. Alternative Response Criteria (Choi, European association for the study of the liver, and modified Response Evaluation Criteria in Solid Tumors [RECIST]) Versus RECIST 1.1 in patients with advanced hepatocellular carcinoma treated with sorafenib. Oncologist 2014;19:394-402.
4. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502-9; discussion 509-11.
5. Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncol 2008;9:962-72.
6. Bullock K, Blackwell K. Clinical efficacy of taxane-trastuzumab combination regimens for HER-2-positive metastatic breast cancer. Oncologist 2008;13:515-25.
7. Siegel AB, Olsen SK, Magun A, et al. Sorafenib: where do we go from here? Hepatology 2010;52:360-9.
8. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
9. Cheng AL, Kang YK, Chen Z, 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;10:25-34.
10. Spangenberg HC, Thimme R, Blum HE. Targeted therapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2009;6:423-32.
11. Rudalska R, Dauch D, Longerich T, et al. In vivo RNAi screening identifies a mechanism of sorafenib resistance in liver cancer. Nat Med 2014;20:1138-46.
12. Wu FQ, Fang T, Yu LX, et al. ADRB2 signaling promotes HCC progression and sorafenib resistance by inhibiting autophagic degradation of HIF1α. J Hepatol 2016;65:314-24.
13. Zhou SL, Zhou ZJ, Hu ZQ, et al. Tumor-Associated Neutrophils Recruit Macrophages and T-Regulatory Cells to Promote Progression of Hepatocellular Carcinoma and Resistance to Sorafenib. Gastroenterology 2016;150:1646-1658.e17.
14. Curtit E, Thiery-Vuillemin A, Nguyen T, et al. Complete histologic response induced by sorafenib in advanced hepatocellular carcinoma: a case report. J Clin Oncol 2011;29:e330-2.
15. Nakano N, Kawaoka T, Aikata H, et al. Complete response to short-term sorafenib treatment alone for hepatocellular carcinoma with bone, lymph node and peritoneum metastases. A case report. Hepatol Res 2016. [Epub ahead of print].

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