

IN THE SPOTLIGHT

VEGFA Genomic Amplification Tailors Treatment of HCCs with Sorafenib

Xiaolin Luo and Gen-Sheng Feng

Summary: In this issue of *Cancer Discovery*, Horwitz and colleagues identified a subtype of hepatocellular carcinoma (HCC) bearing *VEGFA* genomic amplification that is particularly sensitive to VEGFA inhibition and is also more sensitive to sorafenib treatment. Taken conjointly, these data suggest that *VEGFA* genomic amplification can be used as a biomarker for personalized treatment of HCC with sorafenib. *Cancer Discov*; 4(6); 640-1. ©2014 AACR.

See related article by Horwitz et al., p. 730 (7).

Liver cancer has moved up the ranks from the third most common cause of cancer-related death to the second, with 0.8 million new patients annually and a 9.1% death rate worldwide, according to the recently released *World Cancer Report 2014* (1). In North America, liver cancer has also shown increasing prevalence (2). Primary liver cancer includes hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), with HCC responsible for 85% of cases worldwide, making it the major type of primary liver cancer (3). HCC treatment implementations vary and depend on cancer stages. For early-stage HCCs, surgical resection is the best choice with an overall survival rate as high as 90% with well-selected patients. However, for advanced-stage disease, options in hand are extremely limited, with sorafenib the only systemic medicine available.

Sorafenib, a small molecule, targets multiple kinases, including VEGFR, PDGFR β , RAF1, and BRAF. Both *in vivo* and *in vitro* experiments have demonstrated its abilities to inhibit tumor-cell proliferation and tumor angiogenesis and to promote apoptosis (4). In 2005, the FDA approved sorafenib for treatment of advanced renal cell carcinoma, and 2 years later, it was approved for treatment of advanced-stage HCC. Unfortunately, sorafenib's therapeutic effects fell short of expectations. Compared with the placebo group, the experimental group exhibited only 2.8 months longer median overall survival. In addition, severe side effects, including weight loss, hypophosphatemia, diarrhea, and hand-foot skin reaction, appeared more frequently in the sorafenib group (5). One possible reason for the mild effect of sorafenib is that some patients were not sensitive to sorafenib treatment, which implies that a more stringent patient selection procedure along with specific predictive biomarkers is urgently

needed to benefit treatment. Indeed, some investigations have already been performed to this end. Although low-baseline hepatocyte growth factor (HGF) and high-baseline soluble c-KIT concentration separately showed a favorable tendency to sorafenib treatment, neither of them approached statistical significance (6). Because sorafenib is used worldwide as standard care for patients with advanced-stage HCC and is the only systemic medicine to show beneficial effect, more effort is warranted to optimize patient selection. In this issue of *Cancer Discovery*, a collaborative report from the laboratories of Ben-Neriah and Pikarsky (7) identified a subtype of HCCs bearing *VEGFA* genomic amplification that was particularly sensitive to VEGFA inhibition. Moreover, patients with HCC with similar amplification respond favorably to sorafenib treatment.

Inflammation and microenvironmental changes are hallmarks of liver cancer. In HCCs, some factors affecting these two hallmarks may be amplified or deleted. To search for these factors, the authors applied array comparative genomic hybridization (aCGH) to HCC samples isolated from *Mdr2*^{-/-} mice, an inflammation-driven HCC mouse model. They found that Chr17qB3 is present among these amplified regions. *VEGFA*, encoding an important cytokine regulating the microenvironment, is located in this region. More importantly, Horwitz and colleagues (7) found that *VEGFA* amplifications also occurred in 11% of human HCC samples. Unsurprisingly, elevated VEGFA protein levels were detected in both tumor extracts and serum samples. Subsequent experiments established that HCCs harboring genomic *VEGFA* amplification were indeed different from those without the amplification. These tumors exhibited higher proliferation index, vessel density, and macrophage content but a lower incidence of fibrosis. All these data indicated that the microenvironment of these tumors indeed changed in correlation with *VEGFA* amplification.

Because VEGFA cannot directly activate hepatocytes efficiently (8), the authors proposed a very interesting macrophage-tumor cell cross-talk model. In this model, VEGFA, secreted by tumor cells, stimulates macrophages to produce more HGF, which acts back on tumor cells and stimulates their proliferation. The data they presented strongly supported this hypothesis. They observed that tumor cells are the major cell type expressing VEGFA, whereas HGF is mainly

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expressed by macrophages. Aligning with these findings, they found that the expression levels of VEGFRs and coreceptors were higher in macrophages, whereas more HGF receptors were expressed in hepatocytes. Interestingly, VEGFA can increase cellular proliferation *in vivo* but not *in vitro*, which further proved that VEGFA was not directly affecting tumor cells but rather communication with macrophages.

As VEGFR is one of the targets of sorafenib, the authors tested whether this drug had a selective advantage in mouse tumors with *VEGFA* genomic amplification. Although they administered sorafenib to mice only for a short period of time, the results were inspiring. Only HCC with *VEGFA* genomic amplification responded to sorafenib treatment and showed decreased proliferation. This conclusion was confirmed by a Hep3B xenograft experiment. Moreover, the authors extended their investigation to human HCC patient samples. A retrospective study of a human cohort showed that a dramatic improvement was observed in the *VEGFA*-amplified group compared with the nonamplified group in sorafenib-treated patients. All these data suggest that genomic *VEGFA* amplification could be a biomarker that predicts HCC patient response to sorafenib treatment.

The findings of Horwitz and colleagues (7) raise a few questions. Llovet and colleagues (6) analyzed patients' serum VEGF levels from the SHARP trial and found that the levels could not predict response to sorafenib. This finding evokes the question of why *VEGFA* genomic amplification is correlated with response to sorafenib but not VEGF serum level. Further investigation is required to address this issue. Nevertheless, this may also be true for other biomarkers for which the serum level cannot predict response but genomic amplification can. Another issue about Horwitz and colleagues' (7) findings is the clinical practicality. Advanced HCC is usually diagnosed with CT and MRI but not biopsy (9), which makes using *VEGFA* genomic amplification as a biomarker not practicable in the clinic. One possible solution is to isolate circulating tumor cells and sequence their genome to check whether there is *VEGFA* amplification. However, taking into consideration the heterogeneity of the tumors and the relatively small number of circulating tumor cells in blood, many technical problems need to be tackled before clinical use.

The first high-throughput DNA sequencing analyzer MiSeqDx system from Illumina was approved by the FDA last year. This breakthrough technology enables physicians to comprehensively obtain a patient's genetic data much more easily and quickly than before. With this information, combined with research data, doctors will be able to predict a patient's response to a specific treatment more accurately, which will finally help to realize personalized medicine. As suggested by the study by Horwitz and colleagues (7), patients with HCC bearing *VEGFA* genomic amplification may benefit more from sorafenib, but patients without *VEGFA* genomic amplification may only suffer from severe pain caused by side effects. A comprehensive genomic analysis can identify

whether *VEGFA* is amplified in a patient's HCC tumor, providing information for the doctor's decision regarding use of sorafenib.

At the end of 2013, sorafenib was approved by the FDA for advanced thyroid cancer, in addition to kidney cancer in 2005 and HCC in 2007. The NCI website shows that clinical trials of sorafenib for other cancers, including lung cancer, melanoma, and prostate cancer, are on the way. One can expect that the list of cancers that sorafenib can target will be extended in the future. However, considering the pain caused by its side effects and the economic burden of its cost, the selection of patients who are suitable for sorafenib therapy is becoming an even bigger challenge. Taken together, the identification of specific biomarkers that predict response to sorafenib treatment for advanced-stage cancers, as done by Horwitz and colleagues (7) in this study, is worthy of more resources and efforts. Finally, the surprising anti-oncogenic roles of pro-oncogenic molecules recently identified in animal HCC models call for the design of therapeutic strategies for patients with HCC by targeting secondary pathways activated in response to blockade of the primary oncogenic events (10).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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