Title

VEGFA Genomic Amplification Tailors Treatment of HCCs with Sorafenib

Journal

Cancer Discovery, 4(6)

ISSN

2159-8274

Authors

Luo, Xiaolin

Feng, Gen-Sheng

Publication Date

2014-06-01

DOI

10.1158/2159-8290.cd-14-0406

Peer reviewed

HHS Public Access

Author manuscript

Cancer Discov. Author manuscript; available in PMC 2015 November 04.

Published in final edited form as:

Cancer Discov. 2014 June ; 4(6): 640–641. doi:10.1158/2159-8290.CD-14-0406.

VEGFA Genomic Amplification Tailors Treatment of HCCs with Sorafenib

Xiaolin Luo and **Gen-Sheng Feng**

Department of Pathology, and Division of Biological Sciences, University of California San Diego, La Jolla, California, USA 92093-0864

Summary

In this issue of *Cancer Discovery*, Horwitz and colleagues identified a subtype of HCC bearing *VEGFA* genomic amplification that is particularly sensitive to VEGFA inhibition and 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.

Liver cancer has moved up the rank from the third most common cause of cancer death to the second, with 0.8 million new patients annually and a 9.1% death rate worldwide in the recently released *World Cancer Report 2014* (1). In North America, liver cancer has also shown increasing prevalence (2). Primary liver cancer includes hepatocelluar 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, PDGFRβ, RAF11 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 two years later it was approved for treatment of advanced-stage HCC. Unfortunately, sorafenib's therapeutic effects fell short of expectations. Compared to the placebo group, the experimental group only exhibited 2.8 months longer median overall survival. Additionally, 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 are urgently needed to benefit treatment. Indeed, some investigations have already been performed to this end. Although low baseline HGF and high baseline s-c-KIT concentration

Corresponding Author: Gen-Sheng Feng, Department of Pathology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0864. Phone: 858-822-5441; gfeng@ucsd.edu.

Disclosure of potential conflicts of interest: The authors declare no competing financial interests.

separately showed favorable tendency to sorafenib treatment, neither of them approached statistical significance (6). Because sorafenib is used worldwide as a standard care for advanced-stage HCC patients and is the only systemic medicine to showbeneficial effect, more effort is warranted to optimize patient selection. In this issue of *Cancer Discovery*, a collaborative report from the labs of Ben-Neriah and Pikarsky identified a subtype of HCCs bearing *VEGFA* genomic amplification that was particularly sensitive to VEGFA inhibition(7). Moreover, HCC patients with similar amplification are 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 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 with 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 crosstalk 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, while HGF is mainly expressed by macrophages. Aligning with these findings, they found that the expression levels of VEGFRs and co-receptors 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 cell 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 just administered sorafenib to mice 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 to the non-amplified 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 raise a few questions. Josep and colleagues analyzed patients' serum VEGF levels from the SHARP trial and found that it could not predict response to sorafenib (6). This 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 be also true for other biomarkers for which the serum level cannot predict response but genomic amplification can. Another issue regarding Horwitz and colleagues' findings is the clinical practicality. Advanced HCC is usually diagnosed with computed tomography (CT) and magnetic resonance imaging (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 consideration of 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 usage.

The first high-throughput DNA sequencing analyzer MiSeqDx system from Illumina was cleared by the FDA last year. This breakthrough technology enables physicians to comprehensively obtain a patient's genetic data much easier and faster 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 realize personalized medicine. As suggested by the study of Horwitz et al. 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 (7). A comprehensive genomic analysis can identify whether *VEGFA* is amplified in a patient's HCC tumor, providing information for the doctor in his decision for usage of sorafenib.

At the end of 2013, sorafenib was approved by 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 challenge of selecting patients who are suitable for sorafenib therapy is becoming even bigger. Taken together, identifying specific biomarkers predicting response to sorafenib treatment for advanced-stage cancers, as done by Horwitz and colleagues in this study, is worthy of more resources and efforts. Finally, the anti-oncogenic roles of pro-oncogenic molecules recently identified in animal HCC models call for design of therapeutic strategies for HCC patients by targeting activated pathways to block the primary oncogenic events (10).

References

1. S, BW.; W, CP. World Cancer Report 2014. IARC; 2014.
2. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011; 365:1118–27. [PubMed: 21992124]
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003; 362:1907–17. [PubMed: 14667750]
4. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor

tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004; 64:7099–109. [PubMed: 15466206]

5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378–90. [PubMed: 18650514]
6. Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2012; 18:2290–300. [PubMed: 22374331]
7. Horwitz E, Stein I, Andreozzi M, Nemeth J, Shoham A, Pappo O, et al. Human and mouse VEGFA-amplified hepatocellular carcinomas are highly sensitive to sorafenib treatment. Cancer Discovery. 2014
8. LeCouter J, Moritz DR, Li B, Phillips GL, Liang XH, Gerber HP, et al. Angiogenesis-independent endothelial protection of liver: role of VEGFR-1. Science. 2003; 299:890–3. [PubMed: 12574630]
9. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut. 2003; 52(Suppl 3):iii1–8. [PubMed: 12692148]
10. Feng GS. Conflicting roles of molecules in hepatocarcinogenesis: paradigm or paradox. Cancer Cell. 2012; 21:150–4. [PubMed: 22340589]