REVIEW

Mechanisms of resistance to sorafenib and the corresponding strategies in hepatocellular carcinoma

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Abstract

Sorafenib, the unique drug as first-line treatment for advanced hepatocellular carcinoma (HCC), has opened a window of hope after searching for effective agents to combat HCC for decades. However, the overall outcomes are far from satisfactory. One of the explanations is the genetic heterogeneity of HCC, which has led to identifying predictive biomarkers for primary resistance to sorafenib, and then applying the concept of personalized medicine, or seeking therapeutic strategies such as combining sorafenib with other anticancer agents. Some of the combinations have demonstrated a better effectiveness than sorafenib alone, with good tolerance. The acquired resistance to sorafenib has also drawn attention. As a multikinase inhibitor, sorafenib targets several cellular signaling pathways but simultaneously or sequentially the addiction switches and compensatory pathways are activated. Several mechanisms are involved in the acquired resistance to sorafenib, such as crosstalks involving PI3K/Akt and JAK-STAT pathways, hypoxia-inducible pathways, epithelial-mesenchymal transition, *etc*. Based on the investigated mechanisms, some other molecular targeted drugs have been applied as second-line treatment for treat HCC after the failure of sorafenib therapy and more are under evaluation in clinical trials. However, the exact mechanisms accounting for sorafenib resistance remains unclear. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms and help to find effective strategies for overcoming sorafenib resistance in HCC.

Core tip: The primary resistance of hepatocellular carcinoma (HCC) to sorafenib is due to genetic heterogeneity. Thus, seeking predictive biomarkers and combining sorafenib with other anticancer agents for HCC have been launched with varying degrees of success. Sorafenib inhibits several kinase targets but it can also simultaneously or sequentially activate the addiction switches and compensatory pathways, inducing acquired resistance. Some other molecular targeted drugs have been used as second-line treatment for advanced HCC after the failure of sorafenib therapy. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms accounting for sorafenib resistance in HCC.

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INTRODUCTION

Liver cancer is the second most frequent cause of cancer

death in men worldwide and hepatocellular carcinoma (HCC) accounts for 70%-85% of the total liver cancer burden[1]. Many lines of clinical investigation indicate that none of the adjuvant therapies is particularly effective in treating HCC after surgery and systemic traditional chemotherapy has a very low response rate for HCC. Recently emerging molecular targeted drugs (MTD) have been demonstrated to be promising agents in prolonging the overall survival (OS) of late stage HCC patients. Particularly, sorafenib has been uniquely recommended as the first line treatment for advanced HCC[2]. Despite the encouraging achievement, the worry about drug resistance to sorafenib is increasing as the OS of HCC patients after sorafenib treatment was only 2-3 mo longer than placebo and sorafenib was shown to result in a limited increase in median time to symptomatic progression and a low partial response rate due to drug resistance[3,4]. Although the exact rate of resistance to sorafenib has not been reported, considering the dilemma that no effective systemic therapy is available so far for patients after failure of sorafenib therapy, studies on the mechanisms of sorafenib resistance are urgently required[5-7]. The present article aims to review the latest progress in this field by focusing on the mechanisms of resistance to sorafenib and the strategies in HCC.

PREDICTION OF SORAFENIB SENSITIVITY

Due to genetic heterogeneity, some HCC cells are initially resistant to sorafenib, which is termed primary resistance[8]. The IC_{50} values of growth inhibition of different HCC cell lines by sorafenib *in vitro* showed big variations[9,10]. Thus, it is important to identify predictive biomarkers for primary resistance to sorafenib.

The activation of RAF/mitogen-activated protein kinase (MAPK)/extracellular signaling-regulated kinase (ERK) signal pathway is commonly observed in HCC[11]. Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf, thus inhibiting the RAF/MEK/ERK signaling pathways. It was reported that sorafenib inhibited the phosphorylated ERK (pERK) in HCC PLC/PRF/5 and HepG2 cells[9]. Zhang *et al*[12] reported that the effects of sorafenib on cell proliferation were significantly correlated with basal pERK levels and the U0126, a selective inhibitor of ERK1/2, could reduce the sensitivity of HCC cells to sorafenib through downregulation of pERK. In a phase Ⅱ clinical study of sorafenib, the pERK levels in tumor samples from 33 patients showed the correlation with median time to progress (TTP)[13]. However, the relationship was not validated in the phase Ⅲ trial[14]. It has recently been reported that the c-Jun N-terminal kinase (JNK), another member of MAPK family, can serve as a biomarker to predict the sensitivity to sorafenib[15]. Hagiwara *et al*[15] examined the JNK activity in 39 tumor specimens from advanced HCC before sorafenib treatment and found that the tumors from the non-responder group had higher expression

of phospho-c-Jun and JNK activity. Moreover, the JNK activation correlated with decreased TTP and poor OS. A recent study on patients enrolled in the SHARP trial (the phase Ⅲ, randomized, controlled Sorafenib HCC Assessment Randomized Protocol) investigated predictive biomarkers to sorafenib and showed that the angiogenesis biomarkers Ang2 and VEGF, among ten assessed plasma biomarkers, were independent predictors of the survival of advanced HCC patients. Although the patients with higher soluble c-KIT or lower hepatocyte growth factor (HGF) in sera at baseline showed enhanced survival benefit, neither of them predicted the response to sorafenib[16].

The current available data indicate that candidate biomarkers for sorafenib sensitivity are still of uncertain value. Well-designed prospective clinical studies are required to judge their exact roles in predicting the primary resistance to sorafenib in HCC. In addition, more preclinical studies are also needed to clarify whether the currently known biomarkers are the downstream events of the latent key biomarkers or if these biomarkers vary in individual patients.

MECHANISMS OF ACQUIRED RESISTANCE TO SORAFENIB

Long-term exposure to antitumor drugs often results in reduced sensitivity of the tumor cells to the drug, leading to acquired resistance. Many mechanisms account for acquired resistance to antitumor drugs, such as addiction switching, compensatory pathway because of pathway loops or crosstalk, epithelial-mesenchymal transition (EMT), cancer stem cells, disabling of pro-apoptotic signals, hypoxic microenvironment, *etc*[17-19]. Recently, some studies have also indicated the correlation between these mechanisms and resistance to sorafenib in HCC.

PI3K/Akt pathway and sorafenib resistance

The phosphatidylinositol 3-kinase (PI3K)/Akt and MAPK pathways are the most critical pathways involved in the development and progression of HCC and are activated or overexpressed in a high proportion of HCC tissues. The parallel PI3K/Akt pathway remains unscathed when sorafenib targets the MAPK pathway and tyrosine kinases by inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Ret and c-kit[3]. Considering the existing crosstalk between the PI3K/Akt and MAPK pathways[20], the latent compensatory mechanism of PI3K/Akt pathways in drug resistance to sorafenib has been attracting attention. Sorafenib has been demonstrated to activate Akt and upregulate the phosphorylation of its downstream targets, such as S6K and 4EBP1 in HCC cells[21,22]. A study by Chen *et al*[7] has shown that sorafenib-resistant HCC cells, which were established by long-term exposure to sorafenib, had increased expression of phosphorylated Akt and p85, a regulatory subunit of PI3K, compared with the parental cells. Similarly, the HCC cells with ecto-

pic expression of constitutive Akt also showed resistance to sorafenib. In addition, the resistance to sorafenib could be reversed by gene knockdown of Akt and Akt inhibitor MK-2206. These results indicate that activation of PI3K/Akt pathway may contribute to sorafenib resistance and call for further study in clinical trials.

JAK-STAT pathway and sorafenib resistance
The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway participates in the regulation of cell proliferation, differentiation, survival, motility and apoptosis in many organs, including liver[23,24]. STAT3 plays a critical role in transcriptional regulation of genes and is also activated by many cytokines and growth factor receptors, such as PDGFR, fibroblast growth factor receptor (FGFR) and epidermal growth factor receptor (EGFR) through JAK[25,26]. The negative regulation of STAT3 is mainly executed by suppression of cytokine signaling (SOCS) proteins through JAK and Src-homology protein tyrosine phosphatases (SHPs), such as SHP-1 and SHP-2, and cytokines and growth factor receptors[23]. STAT3 is activated in HCC and knockdown of STAT3 had a therapeutic effect on HCC[27]. It has recently been reported that sorafenib inhibited the activity of STAT3 by downregulating the phosphorylation of STAT3 at the tyrosine and serine site (Y705 and S727) through regulating PI3K/Akt pathway and MAPK pathway, respectively, but had no effect on JAK2 and SHP2 expression[27]. Sorafenib displayed its inhibitory effect on STAT3 in an SHP-1-dependent manner, but not kinase-dependent inactivation of STAT3[28]. Sorafenib also overcomes TRAIL resistance by inhibiting the activation of STAT3 in HCC cells[29]. Several studies have also investigated the role of JAK-STAT pathway in the mechanisms of acquired resistance to sorafenib in HCC. Sorafenib-resistant HCC cells express higher levels of p-STAT3, p-JAK1 and p-JAK2, but lower levels of SHP-1 and p-SHP-1, indicating that the JAK-STAT pathway participates in the acquired resistance to sorafenib in HCC[26]. Interestingly, dovitinib, another multikinase inhibitor targeting VEGFR, FGFR and c-KIT and regulating the JAK-STAT pathway, could reverse the acquired resistance to sorafenib by directly activating SHP-1 and thus downregulating p-STAT3[26]. Inhibition of SHP-1 or gene knockdown of *SHP-1* blocked the effect of dovitinib, indicating that the SHP-1-activating agent may provide second-line treatment after the failure of sorafenib therapy[30].

Hypoxic microenvironment and sorafenib resistance
The hypoxic microenvironment is closely related to the resistance to many antitumor drugs[19]. We have previously demonstrated that targeting hypoxia-inducible pathways enhanced the antitumor activity of doxorubicin in HCC[4,31]. Although sorafenib downregulates the synthesis of hypoxia-inducible factor (HIF)-1α in HCC cells *in vitro* and *in vivo*[32], the correlation of sorafenib resistance and hypoxic microenvironment is attractive because the anti-angiogenic activity of sorafenib is speculated to lead to

tumor starvation and subsequent tumor hypoxia[33]. A recent study[34] has shown that sorafenib-resistant HCC tissues had higher expression of HIF-1α than sorafenib-sensitive and pre-treated HCC tissues. In xenograft models, the increased hypoxia because of sustained sorafenib therapy was associated with sorafenib sensitivity. Moreover, EF24, an analogue of curcumin, could synergistically enhance the antitumor effects of sorafenib and overcome sorafenib resistance through inhibiting HIF-1α by sequestering it in cytoplasm and promoting degradation *via* upregulating (von Hippel-Lindau) VHL.

EMT and sorafenib resistance
Epithelial-mesenchymal transition or transformation (EMT) is the transitional phenomenon of epithelial cells to a mesenchymal phenotype which participates in embryonic development and wound healing, and has recently emerged as a pivotal event in the development of the invasive and metastatic potentials of cancer progression, including HCC[35,36]. EMT is regulated by the upstream pathway such as PI3K/Akt pathway, MAPK, *etc*[37]. Emerging evidence suggests that EMT is involved in, and targeting EMT can reverse, the resistance of antitumor drugs[38]. Recently, the role of EMT in the resistance of HCC to sunitinib has been reported[39]. A study showed that sorafenib inhibited the HGF-induced EMT in HCC by downregulating SNAI1 expression *via* the MAPK signaling pathway[37]. The microarray gene expression analysis showed the existence of EMT accompanied by activation of PI3K/Akt and MAPK pathway in sorafenib-resistant HCC cells[40]. The above studies indicate that EMT may be involved in the resistance to sorafenib in HCC but further studies to clarify the specific mechanisms are required.

In addition to the above described mechanisms, some limited studies have also demonstrated that EGFR[10], glucose-regulated protein 78 (GRP78)[41], multidrug resistance protein (MDRP) 2[42], nuclear factor κB (NF-κB)[43,44] and autophagy[45] may be involved in the acquired resistance to sorafenib in HCC.

STRATEGIES FOR OVERCOMING THE RESISTANCE TO SORAFENIB
Although the exact mechanisms of resistance to sorafenib have not yet been fully elucidated, some approaches have been launched to cope with sorafenib resistance in HCC in clinical trials. The completed and ongoing clinical trials for overcoming sorafenib resistance are summarized in Tables 1 and 2, respectively. These trials can be divided into two categories. One is to combine sorafenib with other anticancer drugs and the other is to use other drugs or drug combinations as second-line treatments in HCC patients after the failure of sorafenib therapy.

Combinational therapy with sorafenib
At present, there are dozens of ongoing clinical trials which are evaluating the therapeutic efficacy of sorafenib

Table 1 Completed clinical trials for overcoming sorafenib resistance

Therapeutic strategies	Phases	Cases	Efficacy
Combinational therapy			
5-fluorouracil plus sorafenib[46]	Phase II	39	SD: 46.2%; median TTP: 8 mo; OS: 13.7 mo
Tegafur/uracil plus sorafenib[47]	Phase II	53	Median PFS: 3.7 mo; median OS: 7.4 mo
Octreotide plus sorafenib[48]	Phase II (So.LAR.)	50	SD: 66%; median TTP: 7.0 mo; median OS: 12 mo
Doxorubicin plus sorafenib *vs* doxorubicin plus placebo[50]	Phase III	47 *vs* 49	Median TTP: 6.4 mo *vs* 2.8 mo; OS: 13.7 mo *vs* 6.5 mo; PFS: 6.0 mo *vs* 2.7 mo
Erlotinib plus sorafenib *vs* erlotinib plus placebo[53, 54]	Phase III (SEARCH)	362	Median TTP: 3.2 mo *vs* 4.0 mo; OS: 9.5 mo *vs* 8.5 mo
Second-line treatments			
Sunitinib[55]	Retrospective analysis	11	SD: 40%; median TTP: 3.2 mo
Brivanib[56]	Phase II	46	SD: 41.3%; RR: 4.3%; DCR: 45.7%; median OS: 9.79 mo
Tivantinib *vs* placebo[6]	Phase II	71 *vs* 36	Progressive disease: 65% *vs* 72%; TTP: 1.6 mo *vs* 1.4 mo
Gemcitabine plus oxaliplatin[59]	Retrospective analysis	18	Overall RR: 18.8%; SD: 18.8%; median PFS: 3.2 mo; OS: 4.7 mo
Erlotinib plus bevacizumab[61]	Phase II	10	No response or SD; median TTP: 1.81 mo; OS: 4.37 mo

SD: Stable disease; TTP: Time to progression; OS: Overall survival; PFS: Progression-free survival; DCS: Disease control rate; RR: Response rate.

Table 2 Ongoing clinical trials for overcoming sorafenib resistance

Studies	Therapeutic strategies	Phases	Primary outcomes
Combinational therapy			
NCT01271504	E7050 plus sorafenib *vs* sorafenib	Phase II	Adverse event
NCT01033240	CS-1008 plus sorafenib *vs* sorafenib	Phase II	TTP
NCT01539018	Tegafur-uracil plus sorafenib *vs* sorafenib	Phase II	TTP
NCT01272557	Doxorubicin plus sorafenib *vs* sorafenib	Phase II	TTP
NCT01015833	Doxorubicin plus sorafenib *vs* sorafenib	Phase III	OS
NCT01214343	Cisplatin/fluorouracil plus sorafenib *vs* sorafenib	Phase III	OS
Second-line treatments			
NCT01507168	GC33 *vs* placebo	Phase II	PFS
NCT01273662	Axitinib	Phase II	SD
NCT00717756	Lenalidomide	Phase II	RR
NCT01545804	Lenalidomide	Phase II	SD
NCT01567930	Temsirolimus	Phase II	Disease progression
NCT01180959	Erlotinib plus bevacizumab	Phase II	PFS
NCT01140347	Ramucirumabplus BSC *vs* placebo plus BSC	Phase III	PFS
NCT01108705	Brivanib plus BSC *vs* placebo plus BSC	Phase III	OS
NCT00825955	Brivanib plus BSC *vs* placebo plus BSC	Phase III	OS
NCT01035229	Everolimus plus BSC *vs* placebo plus BSC	Phase III	OS

TTP: Time to progression; OS: Overall survival; SD: Stable disease; PFS: Progression-free survival; RR: Response rate; BSC: Best supportive care.

in combination with other anticancer agents to treat advanced HCC, according to the database of clinical trials from the United States National Institutes of Health (http://www.clinicaltrials.gov). Some completed clinical trials have been promising to some extent by combining sorafenib with other agents.

In a phase II trial with 39 advanced HCC patients, sorafenib in combination with 5-fluorouracil infusion showed an encouraging disease control rate with the stable disease (SD) rate of 46.2% for a median duration of 16.2 mo, median TTP of 8 mo and OS of 13.7 mo[46].

Metronomic chemotherapy using tegafur/uracil has been shown to enhance the anti-tumor effect of anti-angiogenic agents in preclinical models. In a phase II study with 53 advanced HCC patients, metronomic chemotherapy with tegafur/uracil was safely combined with sorafenib and preliminarily showed the improvement of sorafenib efficacy, with median progression-free survival (PFS) of 3.7 mo and median OS of 7.4 mo[47].

In a multicenter phase II So.LAR. study with 50 ad-

vanced HCC patients, the combinational therapy with sorafenib and long-acting octreotide resulted in SD rate of 66%, median TTP of 7.0 mo and median OS of 12 mo[48]. The results suggest that the combination between sorafenib and long-acting octreotide is active and well tolerated in patients with advanced HCC and could represent another efficacious chance for the management of this population[48].

Doxorubicin is considered one of the most effective cytotoxic agents and is widely used in the treatment of HCC, especially *via* transcatheter arterial chemoembolization (TACE)[4,49]. In a phase III trial, doxorubicin plus sorafenib compared with doxorubicin alone was evaluated in 96 patients with advanced HCC[50]. The sorafenib plus doxorubicin achieved longer median TTP (6.4 mo *vs* 2.8 mo), OS (13.7 mo *vs* 6.5 mo) and PFS (6.0 mo *vs* 2.7 mo) than doxorubicin placebo monotherapy. The only grade 2/3 adverse event of left ventricular dysfunction was seen in one patient in the sorafenib plus doxorubicin group. However, because doxorubicin was used as the

controlled arm in this trial, the encouraging outcome was unable to justify that the efficacy was from sorafenib alone or the synergism with doxorubicin. Now, a randomized phase Ⅲ trial aiming to evaluate the combinational therapy of doxorubicin plus sorafenib compared with sorafenib alone is recruiting participants (ClinicalTrials.gov, NCT01840592).

Erlotinib, an oral tyrosine kinase inhibitor of EGFR, has shown a modest antitumor activity against HCC[51,52]. To evaluate the effect of sorafenib in combination with erlotinib, a randomized, placebo-controlled, double-blind, phase Ⅲ study (SEARCH trial, NCT00901901) is being conducted with sorafenib as the controlled arm. However, the preliminary results reported in the 37th European Society for Medical Oncology (ESMO) Congress[53,54] did not show that the addition of erlotinib to sorafenib met the primary endpoint and the median OS and TTP was not statistically different in the experimental and controlled arms.

Second-line treatments
Many anticancer drugs, most of which are MTDs, such as VEGFR inhibitors (axitinib and ramucirumab), mTOR inhibitors (everolimus and temsirolimus), EGFR inhibitor (erlotinib) in combination with VEGFR inhibitor (bevacizumab) and GC33, a recombinant humanized antibody against glypican-3, are being tested as second-line treatments for advanced HCC in clinical trials (http://www.clinicaltrials.gov).

Sunitinib, a multikinase inhibitor targeting the similar receptors to sorafenib, such as VEGFR, PDGFR and RAF, showed a modest antitumor activity in 11 sorafenib-resistant patients with SD in 40% patients and median TTP of 3.2 mo[55]. Undesirably, sunitinib as second-line treatment did not show the antitumor activity in HCC patients with Child-Pugh class B liver cirrhosis because these patients died within 4 mo due to the clinical deterioration of liver function and tumor progression.

Brivanib, a selective dual inhibitor of FGFR and VEGFR, has shown antitumor activity against HCC[56]. A phase Ⅱ open-label study assessed brivanib as second-line treatment in HCC patients who had failed prior to antiangiogenic treatment, including sorafenib[56]. In 46 enrolled patients, brivanib was administered orally at a dose of 800 mg once daily and the SD, tumor response rate and disease control rate was 41.3%, 4.3% and 45.7%, respectively. The median OS was 9.79 mo. The results show that brivanib may be safe and efficient in treating advanced HCC after sorafenib therapy. However, a press release in July, 2012 from Bristol-Myers Squibb, the manufacturer of brivanib, revealed that brivanib did not meet the primary endpoint of improving overall survival *vs* placebo in the phase Ⅲ trial (http://news.bms.com/press-release/).

Recently, a multicenter, randomized, placebo-controlled, double-blind, phase Ⅱ study (ClinicalTrials.gov, NCT00988741) reported the results of using tivantinib, a selective oral inhibitor of MET, as second-line treatment

in sorafenib-resistant HCC[6]. Among the 107 enrolled patients, 104 patients had received sorafenib treatment. Seventy-one patients were randomly assigned to receive tivantinib (38 at 360 mg twice daily and 33 at 240 mg twice daily) and 36 patients to receive placebo. At the time of analysis, 46 (65%) patients in the tivantinib group and 26 (72%) of those in the placebo group had progressive disease. After the median follow-up of 5.5 mo, the tivantinib group had a longer TTP than the placebo group (1.6 mo *vs* 1.4 mo). The 22 (31%) patients with MET-high tumors treated with tivantinib had a median TTP of 2.7 mo, which was significantly longer than that (1.4 mo) for 15 MET-high patients (42%) on placebo. Interestingly, tivantinib at the dose of 240 mg (twice per day) showed slightly longer OS and moderate adverse events compared to the schedule of 360 mg. These results provide an option for second-line treatment of advanced HCC patients, particularly for those with MET-high tumors, after failure of sorafenib and call for further phase Ⅲ trials. The report may also imply that Met might serve as a predictive biomarker in this case.

A drug combination of gemcitabine plus oxaliplatin has shown antitumor activity again HCC[57,58]. Thus, it was used as second-line treatment in HCC patients after sorafenib pretreatment. In a clinical trial with 18 patients after the failure of sorafenib therapy, gemcitabine plus oxaliplatin treatment showed an overall response rate of 18.8%, SD of 18.8%, PFS of the median 3.2 mo and OS of 4.7 mo with moderate adverse events[59].

Erlotinib plus bevacizumab has shown an apparently synergistic effect with acceptable adverse events as first-line treatment of HCC[60]. To evaluate the effects of erlotinib in combination with bevacizumab as second-line therapy after the failure of sorafenib, a phase Ⅱ trial is ongoing (ClinicalTrials.gov, NCT01180959). However, another similar phase Ⅱ trial executed during the same period showed disappointing interim results[61]. Among the ten recruited patients after first-line sorafenib treatment, no response or SD were achieved and the median TTP and OS was 1.81 and 4.37 mo, respectively. Adverse events were common, with rash in 70%, diarrhea in 50% and malaise in 40% of patients. Thus, this trial was halted after the interim analysis[61]. The results of the ongoing similar trial are expected.

CONCLUSION

In summary, the mechanisms accounting for the resistance of HCC to sorafenib are complicated and remain unclear. The primary resistance of HCC to sorafenib is possibly due to the genetic heterogeneity. Seeking predictive biomarkers and therapeutic strategies by combining sorafenib with other anticancer agents have been launched with varying degrees of success. Sorafenib inhibits several kinase targets but it can also simultaneously or sequentially activate the addiction switches and compensatory pathways, such as PI3K/Akt and JAK-STAT pathways, tumor hypoxia, EMT, *etc.*, leading to

acquired resistance. Some other MTDs have been applied as second-line treatment for advanced HCC after the failure of sorafenib therapy and more are under evaluation in clinical trials. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms and effective strategies for overcoming sorafenib resistance in HCC are being sought.

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