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TOPIC HIGHLIGHT

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Role of anti-angiogenesis therapy in the management of hepatocellular carcinoma: The jury is still out

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Abstract

As the leading cause of disease-related deaths, cancer is a major public health threat worldwide. Surgical resection is still the first-line therapy for patients with early-stage cancers. However, postoperative relapse and metastasis remain the cause of 90% of deaths of patients with solid organ malignancies, including hepatocellular carcinoma (HCC). With the rapid development of molecular biology techniques in recent years, molecularly targeted therapies using monoclonal antibodies, small molecules, and vaccines have become a milestone in cancer therapeutic by significantly improving the survival of cancer patients, and have opened a window of hope for patients with advanced cancer. Hypervascularization is a major characteristic of HCC. It has been reported that anti-angiogenic treatments, which inhibit blood vessel formation, are highly effective for treating HCC. However, the efficacy and safety of anti-angiogenesis therapies remain controversial. Sorafenib is an oral multikinase inhibitor with anti-proliferative and anti-angiogenic effects and is the first molecular target drug approved for the treatment of advanced HCC. While sorafenib has shown promising therapeutic effects, substantial evidence of primary and acquired resistance to sorafenib has been reported. Numerous clinical trials have been conducted to evaluate a large number of molecularly targeted drugs for treating HCC, but most drugs exhibited less efficacy and/or higher toxicity compared to sorafenib. Therefore, understanding the mechanism(s) underlying sorafenib resistance of cancer cells is highlighted for efficiently treating HCC. This concise review aims to provide an overview of anti-angiogenesis therapy in the management of HCC and to discuss the common mechanisms of resistance to anti-angiogenesis therapies.

Key words: Hepatocellular carcinoma; Management; Molecularly targeted therapy; Anti-angiogenesis; Sorafenib

Core tip: Hepatocellular carcinoma (HCC) is a devastating disease with a high mortality rate. For a long period of time, no effective treatment options are available for patients with advanced HCC. During the last decade, molecularly targeted therapies have been introduced into the treatment of advanced HCC. However, the efficacy and safety of molecularly targeted therapies remain controversial. In addition, primary or acquired drug resistance limits the activity of molecularly targeted agents, but the underlying mechanisms have not been fully understood. This concise review aims to

provide an overview of anti-angiogenesis therapy in the treatment of HCC.

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INTRODUCTION

Primary liver cancer (PLC) is one of the most common malignancies and the second leading cause of cancer-related deaths around the world. Hepatocellular carcinoma (HCC), the most common type of PLC, accounts for approximate 90% of PLC cases in most countries. In addition, HCC is the 5th and 7th most common cancer in males and females, respectively. The worldwide incidence of HCC is increasing partially due to the rising number of infections caused by hepatitis B virus or hepatitis C virus[1-3]. Recently, while the diagnosis of HCC has been remarkably improved with the use of noninvasive imaging tests, a large number of patients were still diagnosed at the advanced stage due to the lack of symptoms during early stages and the rapid progression of cancer cells[4,5].

The management of HCC depends mainly on tumor stage and liver function reserve. Currently, curative treatments such as surgical resection, liver transplantation, and local ablation can significantly improve the survival of HCC patients at the early stage[2,6]. However for a long period of time, no effective treatment options are available for patients with advanced HCC or who progressed into an advanced stage after other treatments failed. In recent years, molecularly targeted therapies using monoclonal antibodies, small molecules, and vaccines have been widely studied in cancer managements. Given that HCC is a highly vascularized tumor, anti-angiogenic treatments might be highly efficient for the treatment of HCC by inhibiting the formation of blood vessels in cancer tissues through small molecules[7-9].

RESISTANCE TO ANTI-ANGIOGENIC DRUGS OF HCC CELLS

As an oral multikinase inhibitor, sorafenib has both anti-proliferative and anti-angiogenic effects on tumors through blocking Raf and vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase signaling. Sorafenib is the first molecular target drug approved for the treatment of advanced HCC. A phase 3, randomized, double-blind, placebo-controlled, multicenter study was performed in 2008 in 21 Western countries to evaluate the effects of sorafenib on the treatment of HCC. This study showed that sorafenib prolonged the median survival and the time to radiologic progression by approximately 3 mo in advanced HCC patients[10,11]. Cheng *et al*[12] also reported that sorafenib was effective for advanced HCC and was well tolerated in HCC patients from the Asia-Pacific region. In addition, high safety and well-tolerance of sorafenib have been reported in a large phase 4 study including over 1500 patients with unresectable HCC[13,14]. Therefore, sorafenib has been established as the standard first-line monotherapy for patients with advanced HCC[9,15-17]. However, the efficacies of current anti-angiogenesis therapies are still far from satisfactory (Table 1). Currently, the median survival time of HCC patients who received sorafenib treatment is not longer than 1 year even after many years of research[18].

Resistance to molecularly targeted agents including sorafenib is a major reason causing the failure of anticancer therapies (Table 2)[17,19,20]. Primary resistance is observed in some HCC patients who are initially not susceptible to sorafenib therapy due to intrinsic indifference. After long-term exposure, tumor cells may gradually become resistant and/or less susceptible to sorafenib, leading to acquired resistance[17]. Both primary and acquired resistance to sorafenib has been commonly reported in HCC patients[21]. Ezzoukhry *et al*[22] found that HCC cells exhibited different susceptibilities to sorafenib. For example, some HCC cell lines such as Hep3B and SNU-449 were inherently resistant to sorafenib. The authors also showed that activation of the epidermal growth factor receptor (EGFR) was a possible determinant of inherent resistance of HCC cells to sorafenib. In an *in vitro* study, Zhang *et al*[23] showed that phosphorylated extracellular signal-regulated kinase was a potential predictor of sorafenib sensitivity in HCC. Similarly, Blivet-Van Eggelpoël *et al*[21] demonstrated that EGFR and human epidermal growth factor receptor-3 reduced the susceptibility of HCC cells to sorafenib.

The exact molecular mechanisms underlying the acquired resistance to sorafenib are largely unknown[17]. In 2011, Chen *et al*[24] reported that activation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway mediates acquired resistance to sorafenib in HCC cells. Xia *et al*[25] also showed that activation of the transforming growth factor beta-and PI3K/Akt-signaling pathways led to acquired resistance to sorafenib in HCC cells. Recently, a number of studies provided evidence showing that many mechanisms such as cancer stem cells[26-29], epithelial-mesenchymal transition[25,26,28-30], autophagy[31-34], and microenvironment (hypoxic, inflammation, and cytokines)[35-38] were involved in the acquired resistance to anti-angiogenesis therapies of HCC[17,39]. In addition, Zhai *et al*[17] suggested in a review article that sorafenib could simultaneously or sequentially activate the addiction switches and compensatory pathways when its targets were silenced, leading to acquired resistance. Taken together, the exact mechanisms of sorafenib resistance have not been fully elucidated. Therefore, further studies should be conducted to clarify the biological mechanisms, which may further improve the therapeutic effects of sorafenib.

Table 1 Clinical studies on anti-angiogenesis therapy of hepatocellular carcinoma included in this review

Ref.	Year	Phase	Investigational drug	Outcome
Llovet *et al*[10]	2008	Phase 3	Sorafenib	Increased survival
Cheng *et al*[12]	2009	Phase 3	Sorafenib	Increased survival
Lencioni *et al*[13]	2012	Phase 4	Sorafenib	High safety
Lencioni *et al*[14]	2014	Phase 4	Sorafenib	High safety
Johnson *et al*[40]	2013	Phase 3	Brivanib	Less well-tolerated
Cheng *et al*[41]	2013	Phase 3	Sunitinib	Significantly inferior than sorafenib
Zhu *et al*[42]	2012	Phase 3	Sorafenib plus erlotinib	No survival benefit
Llovet *et al*[43]	2013	Phase 3	Brivanib after sorafenib failed	No survival benefit
Zhu *et al*[44]	2014	Phase 3	Everolimus after sorafenib failed	No survival benefit

Table 2 Studies on the mechanisms of anti-angiogenesis therapy resistance in hepatocellular carcinoma

Ref.	Year	Investigational drug	Pathways/genes involved	Effects
Blivet-Van Eggelpoël *et al*[21]	2012	Sorafenib	EGFR and HER-3	Restrict cell response
Ezzoukhry *et al*[22]	2012	Sorafenib	EGFR	Potential determinant of primary resistance
Zhang *et al*[23]	2009	Sorafenib	pERK	Potential biomarker for sensitivity prediction
Chen *et al*[24]	2011	Sorafenib	PI3K/Akt	Mediates acquired resistance
Xia *et al*[25]	2013	Sorafenib	TGF-β-and PI3K/Akt	Mediates acquired resistance
Chen *et al*[26]	2011	Sorafenib	EMT and hedgehog signaling	Drug resistance
Xin *et al*[27]	2013	Sorafenib	CSCs	Drug resistance
Chow *et al*[28]	2013	Sorafenib	EMT	Acquired resistance
Fernando *et al*[29]	2014	Sorafenib	TGF-β pathway	Prediction of low susceptibility
Huang *et al*[30]	2013	Sorafenib	EMT	Drug resistance
Shi *et al*[31]	2011	Sorafenib	Autophagy	Drug resistance
Shimizu *et al*[32]	2012	Sorafenib	Autophagy	Impair antitumor effects
Zhai *et al*[33]	2014	Sorafenib	Autophagy	Acquired resistance
Liu *et al*[34]	2013	Sorafenib	Autophagy	Facilitates resistance
Liang *et al*[36]	2013	Sorafenib	Hypoxia	Drug resistance
Mao *et al*[38]	2014	Sorafenib	microRNA-193b	Enhances cell response
Ebos *et al*[46]	2009	Sunitinib	VEGFR/PDGFR	Accelerate metastasis and decrease overall survival
Pàez-Ribes *et al*[47]	2009	Sunitinib	VEGFR/PDGFR	Increase local invasion and distant metastasis
Xiong *et al*[50]	2009	Sorafenib	TECs	Drug resistance
Li *et al*[53]	2011	Bevacizumab	Dll4-notch signaling	Drug resistance

EGFR: Epidermal growth factor receptor; HER-3: Human epidermal growth factor receptor-3; pERK: Phosphorylated extracellular signal-regulated kinase; PI3K: Phosphatidylinositol 3-kinase; TGF-β: Transforming growth factor beta; EMT: Epithelial-mesenchymal transition; CSCs: Cancer stem cells; TECs: Tumor-derived endothelial cells; VEGFR: Vascular endothelial growth factor receptors; PDGFR: Platelet-derived growth factor receptors; Dll4: Delta-like ligand 4.

The discovery and development of sorafenib have paved the way to the development of new anti-angiogenesis drugs for advanced HCC or for whom sorafenib failed. More recently, many clinical trials are conducted all over the world, but the problem still exists. Due to good results from preclinical and early-phase studies, some other molecularly targeted drugs have been applied as the second-line treatment for advanced HCC when sorafenib treatment fails. In a number of large-scale randomized phase 3 trials, unfortunately, none of them have shown survival benefits in the first-line (brivanib, sunitinib, erlotinib, and linifanib[40-42]) or second-line (brivanib[43], everolimus[44]) setting after sorafenib progression[18,45].

Furthermore, it was proposed that anti-angiogenic therapies may cause tumor progression and metastasis. Ebos *et al*[46] reported that sunitinib (a VEGF receptors/PDGF receptors kinase inhibitor) promoted tumor growth and metastasis after a short-term application. Similarly, Pàez-Ribes *et al*[47] demonstrated that application of angiogenic inhibitors targeting the VEGF signaling pathway elicit malignant progression of tumors to increased local invasion, lymphatic and distant metastasis. Recently, Chow *et al*[28] reported that advanced HCC patients with acquired resistance to sorafenib might have enhanced tumor growth properties or metastatic potentials. Therefore, understanding the molecular mechanisms underlying anti-angiogenesis therapy resistance may allow us to identify key molecular targets for efficient anti-angiogenesis therapy.

NEW MECHANISMS OF RESISTANCE TO ANTI-ANGIOGENIC DRUGS

During the last five years, increasing evidence suggested that tumor-derived endothelial cells (TECs), which exhibit distinct histologic appearance compared to normal endothelial cells (NECs), may contribute to the resistance of anti-angiogenic therapies[48,49]. In 2009, Xiong *et al*[50] reported that TECs in human HCC tissues had higher angiogenic capacity and sorafenib resistance than NECs.

Some researchers have concluded that TECs can acquire molecular cytogenetic abnormalities in tumor microenvironment; however, the molecular mechanisms underlying the resistance of TECs to anti-angiogenic therapies remain largely unknown. Attempts to resolve this dilemma have resulted in the discovery of transdifferentiation of tumor cells to vascular endothelial cells. In 2010, Wang *et al*[51] and Ricci-Vitiani *et al*[52] provided strong evidence showing that a number of TECs that contribute to blood vessels in glioblastoma were transdifferentiated from tumor stem-like cells. Wang *et al*[51] also showed that blocking the VEGF/VEGFR2 signaling pathway inhibited the maturation of tumor endothelial progenitors into endothelia but not the differentiation of tumor stem-like cells into endothelial progenitors, while the initial differentiation of tumor stem-like cells to endothelial progenitor cells was regulated by Notch1. Consistently, Li *et al*[53] reported that Delta-like ligand 4 (Dll4; a novel Notch ligand)-Notch signaling mediated the resistance to VEGF inhibitor bevacizumab and Dll4-expressing tumors were resistant to a VEGFR targeting multikinase inhibitor *in vivo*. Furthermore, it has also been shown that Dll4-mediated Notch signaling played a central role in active vascularization[54] and blockade of Dll4 resulted in tumor growth inhibition even for tumors resistant to anti-VEGF treatments[55].

CONCLUSION

In summary, sorafenib is still the only approved drug for the therapy of advanced HCC. However, the long-term survival benefit from sorafenib treatment is relatively limited. Some other anti-angiogenesis drugs have been evaluated preclinically and clinically for the treatment of HCC, but their effects were not satisfactory. Therefore, identification of novel anti-angiogenic drugs and improvement of the currently available anti-angiogenesis therapies are highlighted for the treatment of HCC.

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