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Abstract

Angiogenesis plays a pivotal role in many pathological processes, including hepatocellular carcinoma (HCC). This indicates that antiangiogenic agents could be promising candidates for chemoprevention against HCC. Several inhibitors targeting receptor tyrosine kinases (RTKs) for the regulation of tumoral vascularization have been developed and employed in clinical practice, including sorafenib. However, there seem to be several issues for the long-term use of this agent as some patients have experienced adverse effects while taking sorafenib. Therefore, it is desirable for patients with chronic liver diseases to be administered sorafenib as little as possible by combining other safe-to-use antiangiogenic compounds. Various factors, such as renin-angiotensin-aldosterone system (RAAS) and insulin resistance (IR), reciprocally contribute to the promotion of angiogenesis. A blockade of RAAS with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-II (AT-II) receptor blocker (ARB) markedly attenuates HCC in conjunction with the suppression of angiogenesis. Moreover, the IR status has demonstrated direct acceleration in the progression of HCC via the augmentation of tumoral neovascularization. These findings suggest that a combination therapy involving a lower dose of sorafenib with other clinically used agents [e.g., RAAS blockers, insulin sensitizer agents, and branched-chain amino acids (BCAA)] may reduce the adverse effects of sorafenib without attenuating the inhibitory effect against HCC in comparison to a high-dose administration.

Keywords: hepatocellular carcinoma, fibrosis, renin-angiotensin system

1. Introduction

Angiogenesis is the development of new vasculature from preexisting blood vessels or circulating endothelial cell (EC) stem cells. Emerging evidence indicates that angiogenesis develops in many organs and under multiple pathologic situations, as well as during conditions...
of tissue growth and regeneration. Abnormal pathological angiogenesis is observed in patients with rheumatoid arthritis, psoriasis, diabetic retinopathy, fibrogenesis, and tumor growth [1]. Although early studies were conducted to determine the molecular processes associated with carcinogenesis and angiogenesis that were performed independently, more recent studies have revealed that both biological phenomena emerge synergistically [2].

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related mortality worldwide, accounting for more than 600,000 new cases annually. The greatest risk factors for developing HCC include liver cirrhosis induced by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, excessive alcohol intake, and metabolic syndrome. Regardless of the etiology, since HCC commonly develops in patients with a chronic liver disease (e.g., liver cirrhosis) only approximately one-third of the patients diagnosed with HCC are eligible for curative treatments (e.g., surgical resection) [3]. Consequently, several alternative therapies have been employed, including percutaneous radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). However, no satisfactory improvement of HCC prognosis has been achieved to date. The notable characteristic of HCC that accounts for its poor prognosis is the risk of high frequency in recurrence attributed to intrahepatic metastasis or the multicentric development. The key feature of HCC progression is also hypervascularity formed by intratumoral angiogenesis as well as the frequent recurrence. Several studies have demonstrated that angiogenesis is implicated in the survival and growth of HCC. It has also been reported that angiogenesis can be induced during the early stages of tumor formation and the various carcinogenic mechanisms have been demonstrated in several different experimental models [4–7]. Therefore, several antiangiogenic agents (i.e., sorafenib) have been developed as novel treatment options for HCC.

In this chapter, mechanistic insights into angiogenesis and its contribution to hepatocarcinogenesis will initially be reviewed. In addition, newly developed antiangiogenic agents will be described in detail.

2. Angiogenesis in HCC

In HCC, tumor angiogenesis leads to a pathologic vascularization pattern, of which intratumoral vascularization is critical for the diagnosis and treatment of HCC, as well as for pathogenesis and patient prognosis [1, 8, 9]. In general, HCC is supplied with blood flow primarily via the hepatic arteries, while noncancerous lesions and the normal liver parenchyma are supplied predominantly by the portal vein. This distinct vascularization is clinically utilized to diagnose HCC radiographically by emphasizing the tumor lesions. Any tumor mass more than 1–2 mm³ depends entirely on the formation of a vascular network that provides the growing tumor with oxygen and essential nutrients [10].

Of the various proangiogenic factors, vascular endothelial growth factor (VEGF) is one of the most potent and required for both physiological and pathological angiogenesis [11]. VEGF induces EC proliferation, promotes migration and differentiation as well as stimulates permeabilization of blood vessels and vasculogenesis. The several forms of VEGF bind to
two tyrosine kinase receptors, \textit{fms}-like tyrosine kinase (flt-1: VEGFR-1) and the kinase insert domain-containing receptor/murine homolog, fetal liver kinase-1 (KDR/Flik-1: VEGFR-2) \cite{11, 12}. Recent reports have demonstrated that upregulated VEGF expression is more frequently observed in the tumor lesions of HCC than noncancerous lesions \cite{13–15}. Moreover, the marked increase of VEGF expression is shown during both hepatocarcinogenesis and HCC growth in accordance with the augmented neovascularization. Our basic studies elucidated that monoclonal antibodies (mAb) against both VEGFR-1 and VEGFR-2 ameliorated the HCC development with antiangiogenic activity in rodents \cite{16}. These findings indicate that a blockade of the VEGF-VEGFR axis contributes to the suppressive effect on HCC development.

In tumor neovascularization, VEGF often coordinates with other angiogenic pathways. The angiopoietins (Ang) bind with receptor tyrosine kinases (RTKs) with immunoglobulin-like and EGF-like domains (Tie1 and Tie2). Increased levels of Ang2 promote tumor angiogenesis, metastasis, and inflammation with augmentation of VEGF activity. VEGF-A is also upregulated by interaction with multiple growth factors, including fibroblast growth factor (FGF), insulin-like growth factor factor-1 (IGF-1), platelet-derived growth factor (PDGF), and the transforming growth factors (TGF) \cite{17}. Tissue hypoxia also stimulates VEGF-A upregulation via the hypoxia-inducible factors (HIF)-1α and HIF-2α \cite{17}.

3. Molecular targeted therapy

Several small-molecule, orally available RTK inhibitors exhibit an antiangiogenic effect of inhibiting VEGF and other kinases. They are expected to have high clinical utility and are currently being tested in clinical trials of varying stages for the treatment of advanced HCC (Table 1).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>A-RAF, B-RAF, C-RAF/Raf1-VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, c-Kit</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR-1, 2, and 3, PDGFR-α, β, c-Kit, Flt3</td>
</tr>
<tr>
<td>Brivanib</td>
<td>VEGFR-1, 2, and 3, FGFR-1, 2, and 3</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>VEGFR-1, 2, 3, FGFR-1, 2, 3, and 4, PDGFR-α, c-Kit, RET</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>VEGFR-2, MET, RET</td>
</tr>
</tbody>
</table>

Table 1. Molecularly targeted antiangiogenic agents for advanced HCC.

3.1. Sorafenib

Sorafenib (Nexavar®) was developed in 1995 and is the only chemotherapeutic drug that has demonstrated to improve the survival rate in patients with HCC \cite{18, 19}. Sorafenib acts by inhibiting the RAF serine/threonine kinases that play a key role in the transduction of mitogenic and oncogenic pathways through the Raf/mitogen-activated protein kinase (MEK)/
extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathway [20]. Such signaling results in a lower cyclin D1 expression as well as cell cycle arrest. Sorafenib also potently inhibits VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, and c-Kit, which promote angiogenesis [19, 20]. The repression blocks a broad spectrum of different processes involved in proliferation, angiogenesis, or apoptosis, causing a reduction in the blood vessel regions of the tumor and the starving of cancerous cells. Furthermore, sorafenib enhances tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced cell death through an SH2 domain, which causes a tyrosine phosphatase (SHP-1)-dependent reduction of signal transducers and activators of transcription type 3 (STAT3) phosphorylation and the related protein myeloid cell leukemia 1 (Mcl-1) (i.e., survivin and cyclin D1) in HCC cells [21]. Sorafenib is also able to repress Mcl-1 activity through an MAPK-independent mechanism, which increases the intrinsic apoptosis pathway in tumor cells. Moreover, recent studies have claimed that the eukaryotic translation initiation factor 4E (eIF4E) might be implicated in sorafenib-dependent Mcl-1 inhibition [22]. Clinically, sorafenib can extend the mean patient survival from 7.9 to 10.7 months [19]. Representative adverse events caused by the treatment of sorafenib consist of diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia. Currently, sorafenib is the first and only agent to demonstrate a beneficial overall survival (OS) and be approved by regulators globally in patients with advanced HCC [19].

3.2. Sunitinib

Sunitinib (Sutent®) is an oral multi-RTK inhibitor targeting VEGFR-1, 2, and 3, PDGFRs, c-Kit, and other RTKs associated with angiogenesis [23]. Several phase II clinical trials have shown favorable results regarding the antitumor activity of this drug against advanced HCC. In one phase III trial, the median OS was 7.9 and 10.2 in the sunitinib and sorafenib groups, respectively [24]. This indicates that sunitinib had no benefit over sorafenib as a first-line therapy for advanced HCC.

3.3. Brivanib

Brivanib, a dual tyrosine kinase inhibitor, shows potent and selective inhibition of VEGFR and FGFR [25]. Brivanib has exerted an anticancerous effect in xenograft human HCC models expressing FGF receptors [26]. Two phase III trials have been performed: (1) the BRISK-FL study, in which brivanib vs. sorafenib as first-line therapy was evaluated in patients with advanced HCC and (2) the BRISK-PS study, in which brivanib was administered to patients with advanced HCC who were resistant to sorafenib [27, 28]. However, both trials failed to meet the primary endpoint of statistically improving the OS rate.

3.4. Lenvatinib

Lenvatinib (Lenvima®) is an oral multityrosine kinase inhibitor with potent antiangiogenic effects that has recently been approved for use in differentiated thyroid cancer [29]. The drug was established in patient-derived xenograft models that reliably recapitulated the genetic and phenotypic features of HCC [30]. Moreover, in models expressing high levels of FGF receptor
1, lenvatinib exhibited a greater efficacy than sorafenib. Lenvatinib has also shown highly promising data in phase I/II clinical trials involving patients with advanced HCC [31].

3.5. Cabozantinib

Cabozantinib (Cometriq®) was approved in 2012 by the FDA and is a small-molecule RTK inhibitor with potent activity toward VEGFR-2, MET, and RET (rearranged during transfection), leading to the inhibition of tumor angiogenesis [32]. In a phase II study, the observed disease control rate following 12 weeks of treatment with cabozantinib was found to be 68 or 78% of the patients with or without prior sorafenib treatment exhibited tumor regression. A phase III randomized double-blind, controlled trial is ongoing to compare the efficacy of cabozantinib with a placebo as the second-line treatment modality for advanced HCC patients who have previously received sorafenib.

4. Alternative therapy

Sorafenib is the standard therapeutic agent administered for the treatment of advanced stages of HCC and it is likely that other RTK inhibitors will also become commonly utilized drugs. However, chronic liver damage usually lowers the capacity of drug metabolism in patients, and the long-term administration of sorafenib may induce excessive adverse effects. Therefore, to reduce dosage of sorafenib, an alternative approach may be required to identify a clinically available compound targeting tumor angiogenesis. Among the various factors to affect angiogenic activities, many researchers have focused their attention on the mechanisms of angiotensin-II (AT-II) and insulin resistance (IR). These factors have been shown to affect angiogenesis in the liver via close interactions [33]. Moreover, since these factors could also be involved in the HCC, the regulation of these factors might contribute to suppressing the progression of the chronic liver disease.

4.1. RAAS blockers

The renin-angiotensin-aldosterone system (RAAS) is a hormone system that is involved in the regulation of the plasma sodium concentration and arterial blood pressure to maintain body fluid homeostasis [34]. Recent reports have demonstrated that RAAS is locally expressed in a number of tissues, including the kidneys, adrenal glands, heart, vasculature and nervous system, and liver. Actually, RAAS is frequently activated in patients with chronic liver diseases, such as liver cirrhosis [35, 36]. AT-II is an octapeptide derived from its precursor, AT-I, after AT-I converting enzyme (ACE) acts AT-I, proteolytically cleaving the C-terminal dipeptide. During the progression of chronic liver diseases, AT-II is considered to be a potential mediator of portal hypertension. It has been reported that AT-II plasma levels are clinically increased in patients with cirrhosis, and an animal study has shown the elevation of the portal pressure by AT-II administration [37, 38].

AT-II plays a crucial role in the development of several cancers, including HCC. Lever et al. has previously shown the outcome of a retrospective cohort study consisting of 5207 patients...
with treatment of either an ACE inhibitor (ACE-I) or other antihypertensive agents such as calcium channel blockers, diuretics, and β-blockers with a 10-year follow-up (Glasgow study). Interestingly, in their study, the incidence of cancer and fetal cancer was decreased in the patients with ACE-I treatment as compared with those with other drugs [39]. A recent cohort study has also demonstrated a lower incidence of cancer in patients using ACE-I or an AT-II receptor blocker (ARB) than nonusers [40]. Furthermore, it has been reported that the addition of ACE-I or ARB provided the prolonged survival for the patients with advanced non–small cell lung cancer undergoing platinum-based chemotherapy [41]. Additionally, inhibition of RAAS possibly exerted the beneficial effects on the prognosis of patients with advanced hormone-refractory prostate cancer and pancreatic cancer receiving gemcitabine [42, 43]. In regard to liver cancer, ACE-I showed the suppressive effect on the tumor growth in a murine HCC experimental model [44].

The RAAS, especially AT-II, is potently involved in the regulation of both rarefaction and expansion of the vascular network. Circulating AT-II leads to drive a variety of signaling cascades leading to VEGF, FGF, IGF, and TGF-β expression through mainly binding to the AT1R on ECs [45–47]. AT-II/AT1-R axis plays a key role in the regulation of angiogenic activity in various pathological events, including tumor neovascularization. Actually, inhibition of AT-II by ACE-I and ARB reportedly attenuates intratumoral neovascularization with down-regulation of VEGF expression in several cancers [48–50]. These findings indicate that ACE-I and ARB can be candidates for novel antiangiogenic agents against HCC. However, previous report has suggested that monotherapy with only antiangiogenic agent does not exert the sufficient effect on the prognosis in patients with advanced cancer [51]. Therefore, the combination treatment of antiangiogenic agents has been approached to show a synergistic inhibitory effect on cancer progression [51, 52]. For example, the combination of ACE-I and interferon (IFN) suppressed HCC growth more potently than monotherapy with ACE-I [53]. Our report demonstrated that the antitumoral effect of 5-fluorouracil (5-FU) is also enhanced by combination with ACE-I [54].

As well as tumor growth and metastasis, the early stages of carcinogenesis are also regulated by RAAS-mediated angiogenesis [5, 55]. Our animal study has shown that ACE-I significantly suppressed hepatocarcinogenesis at a clinically comparable low dose together with an attenuated neovascularization [56]. Additionally, a combination of ACE-I with supplementation of vitamin K (VK), which is often administered to the patients with osteoporosis, showed a more potent inhibitory effect on rat hepatocarcinogenesis than ACE-I monotherapy [57]. This combination regimen consisting of ACE-I and VK also exhibited the beneficial effect on ameliorating hepatocarcinogenesis in our clinical study [58]. A 48-month follow-up study revealed that a combined ACE-I with VK significantly suppressed the cumulative recurrence of HCC with reduced serum VEGF levels. The serum level of lectin-reactive α-fetoprotein (AFP-L3), known as one of the HCC tumor markers, was also decreased in parallel with VEGF. Accordingly, this combination regimen may represent a new strategy for chemoprevention against HCC.

Aldosterone (Ald), a downstream component of AT-II in RAAS, also affects in the regulation of angiogenesis. Endocrinologically, Ald is a mineralocorticoid hormone regulating the
plasma sodium (Na\(^{+}\)), the extracellular potassium (K\(^{+}\)) and arterial blood pressure, blood pressure, and electrolyte balance via mineralocorticoid receptors (MR) [59]. Recent data have suggested that Ald plays a key role in endothelial dysfunction, as well as a suggested involvement in the pathogenesis of hypertension [60]. Moreover, the possible involvement of Ald and the MR systems in pathological ocular neovascularization has been reported [61]. Ald was shown to stimulate the proliferation and tubulogenesis of EC, and exacerbated angiogenesis in oxygen-induced retinopathy. In addition, these events could be attenuated by spironolactone. Eplerenone, a selective Ald blocker (SAB), is clinically used as a novel option for the treatment of hypertension. SAB is a selective MR antagonist with higher affinity than spironolactone, contributing to lower side effect by binding the progesterone and androgen receptors. The animal study revealed that murine hepatocarcinogenesis was markedly suppressed by the treatment of SAB with attenuation of VEGF-mediated angiogenesis [62]. These results indicate that SAB is also a viable option for treatment of HCC.

4.2. Regulation of insulin resistance

Recent studies have revealed a close relationship between IR and the progression of liver disease, including HCC [63, 64]. In general, chronic liver diseases impair the metabolic homeostasis of glucose as a result of IR, glucose intolerance, and DM [65]. Several clinical studies have also identified the hyperinsulinemia in patients with chronic hepatitis C (CHC) [66–68]. Experimental evidence with the HCV-transgenic mouse model confirms the contribution of HCV in the development of IR and DM [69]. In this model, the overproduced TNF-\(\alpha\) appears to play a pivotal role in the induction of IR and DM. TNF-\(\alpha\) is a proinflammatory cytokine, dramatically elevated during inflammation-induced disease pathology. HCV itself induces the phosphorylation of the serine residues associated with the insulin receptor substrate (IRS)-1 and -2 and stimulates the overproduction of suppressor of cytokine-3 (SOC-3), inhibiting the phosphorylation of Akt/PI3K, leading to the blockade of transactivation of GLUT-4, which contributes to inhibit intracellular glucose uptake. Additionally, nonalcoholic fatty liver disease (NAFLD) is a common liver disorder associated with IR and DM [70]. Various factors participate in the progression of NAFLD, such as oxidative stress, endotoxemia, obesity, genetic factors, and IR. Several reports have suggested the association of IR and mitochondrial abnormalities [71].

Recently, a reciprocal relationship between diabetes and HCC has been noticed. A two to threefold increase in the risk of HCC has been observed in the patients with DM, regardless of the etiology of chronic liver diseases [72–74]. A large longitudinal study in the United States demonstrated the twofold higher incidence of HCC in the diabetic patients [74]. Moreover, a recent study has elucidated that the IR status directly facilitated hepatocarcinogenesis [64]. Hyperinsulinemia can generally induce the synthesis and activation of IGF-1, which has a potential to progress a variety of cancer [75]. The altered expression pattern of IGF-1 signaling has been found in human HCC as well as hepatocarcinogenesis in rodent models [76]. Furthermore, IR status may progress hepatocarcinogenesis through the augmentation of hepatic neovascularization and VEGF expression in a rat carcinogenesis model [64].
The diabetic patients with compensated liver diseases initially are treated by a lifestyle change. However, restrictive diets may be liable to aggravate malnutrition in some patients. Thus, the oral antidiabetic drugs are administered to treat the diabetic patients with advanced liver diseases such as cirrhosis [77, 78]. To avoid hyperinsulinemia affecting adversely HCC growth, the drugs exerting insulin-sensitizing effects are preferable such as metformin, pioglitazone, dipeptidyl peptidase 4 inhibitor, or sodium glucose cotransporter inhibitor. Another report has demonstrated that the use of statins, a class of lipid-lowering medications by inhibiting HMG-CoA reductase that plays a central role in the production of cholesterol, significantly lowered the risk of HCC in the patients with DM [79].

The branched-chain amino acid (BCAA), an amino acid having aliphatic side chains with a branch (a central carbon atom bound to three or more carbon atoms), comprises three essential amino acids: leucine, isoleucine, and valine. Several clinical studies have suggested the beneficial effect of the long-term supplementation with BCAA granules on hypoalbuminemia and event-free survival in the patients with cirrhosis [80, 81]. BCAAs have also been shown to induce glucose uptake and improve glucose metabolism in a rat cirrhotic model. Intriguingly, the animal study using obese diabetic rat showed a chemopreventive effect of BCAAs against HCC with the downregulation of VEGF and antiangiogenic activity [82, 83]. Multicenter study in Japan also revealed that BCAAs decreased the incidence of HCC in patients with HCV-related cirrhosis as well as the type 2 DM and obesity [84]. However, a monotherapy with BCAA did not inhibit the recurrence of HCC after curative treatment. Therefore, to utilize BCAAs with sufficient effect against HCC, it is strongly recommended to combine them with other drugs. From previous research, AT-II also plays a key role in the development of IR. Actually, mice genetically lacking ACE exhibited the improvement of glucose tolerance through the reduced fat mass [85]. Moreover, additional administration of ACE-I or ARB to BCAAs is also shown to improve the IR status [33, 86]. Our randomized control trial study demonstrated that the combined BCAAs with ACE-I suppresses the cumulative recurrence of HCC in the patients with IR [87].

Taken together, these findings indicate that the combination of BCAAs supplementation and RAAS blockade may represent a potentially novel therapeutic strategy against HCC in the patients with IR.

5. Conclusions and future perspectives

Angiogenesis plays a crucial role in hepatocarcinogenesis and HCC progression, indicating the requirement of an antiangiogenic therapy as a tool for suppressing HCC. Sorafenib has become a breakthrough drug in the field of HCC, with an improvement in the median survival of almost 3 months. This represents a reduction of greater than 30% for the probability of death during the follow-up period.

However, when using RTK inhibitors, including sorafenib for patients with chronic liver diseases, many patients exhibit adverse effects, and several symptoms are very severe. Since the adverse effects induced by RTK inhibitors emerge in a dose-dependent manner, it is
desirable for patients with chronic liver diseases to avoid these drugs as much as possible. Therefore, to lower the dose of such treatments, a clinically available compound to use in combination with RTK inhibitors may be required.

ACE-I, ARB, and SAB are extensively employed as antihypertensive agents in clinical practice without serious adverse effects. Thus, these RAAS blocking agents may provide a novel strategy targeting HCC. However, several reports also suggest that there is a close relationship between AT-II polymorphisms and the progression of chronic liver diseases and cancers. In certain types of cancers, the elevated ACE genetic polymorphisms are significantly involved in their poor prognosis [88, 89]. Additionally, AT-II type I receptor polymorphism reportedly contributes to the occurrence of nonalcoholic steatohepatitis (NASH) [90]. These evidences suggest that the efficacy of RAAS inhibition may vary in each case. Since combination treatment of ACE-I and VK exerted substantially more potent inhibitory effects, a combination treatment involving these agents may be preferable for future clinical applications. Furthermore, under IR conditions, the combination treatment of BCAA and ACE-I would be a promising approach against HCC via the suppression of VEGF-mediated angiogenesis. Since these agents are widely used in clinical practice, the combination of these agents with RTK inhibitors such as sorafenib represents a potential alternative approach against HCC.

Author details

Kosuke Kaji and Hitoshi Yoshiji

*Address all correspondence to: kajik@naramed-u.ac.jp

Third Department of Internal Medicine, Nara Medical University, Shijo-cho, Kashihara, Nara, Japan

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