Apatinib as an alternative therapy for advanced hepatocellular carcinoma

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Apatinib, as a tyrosine kinase inhibitor, has a good inhibitory effect on angiogenesis. Registered tyrosine kinase inhibitors targeting vascular endothelial growth factor reduce angiogenesis. Apatinib, a tyrosine kinase inhibitor, can specifically inhibit vascular endothelial growth factor receptor 2, showing encouraging anti-tumor effects in a variety of tumors including advanced hepatocellular carcinoma (HCC). This article intends to review the clinical research and application prospects of apatinib in the field of HCC.

Key Words: Apatinib; Hepatocellular carcinoma; Angiogenesis; Vascular endothelial growth factor receptor 2

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advanced hepatocellular carcinoma (HCC). In this article, we will introduce the role of apatinib in advanced HCC from the aspects of structure and mechanism, pharmacokinetics, preclinical studies, clinical trials, side effects, and combined drug use.

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INTRODUCTION
Hepatocellular carcinoma (HCC) is the third most common malignant tumor in China. Its 5-year survival rate is only 14.1%, which seriously threatens people's health and life[1]. Asymptomatic or insignificant symptoms are common in the early course of the disease. About 70%-85% of patients are in advanced stage at the time of diagnosis[2], and the natural survival time is only 4.2 mo in the Asia-Pacific region and 7.9 mo in Europe[3]. For patients who have no opportunity for surgery or metastasis after treatment, effective systemic treatment is necessary.

In the "Guidelines Insights: Hepatobiliary Cancers, Version 2.2019", first-line targeted drugs for palliative systemic therapy include sorafenib and lenvatinib[4]. As a multi-target kinase inhibitor, sorafenib can inhibit the proliferation of HCC cells through the RAF/MEK/ERK signaling pathway and block the angiogenesis by inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptors (PDGFRs)[6]. Two phase III clinical trials confirmed that sorafenib prolonged the overall survival (OS) by 2.3-3.2 mo, while the objective response rate (ORR) was 2% to 3.3%[6,9]. The effect of lenvatinib is not inferior to sorafenib, while OS and progression free survival (PFS) are improved compared with the latter. However, the therapeutic effect is still not very satisfying[10].

Apatinib mesylate (YN968D1) is a highly specific small molecule VEGFR-2 tyrosine kinase inhibitor, preventing its downstream signaling pathways, blocking the migration and proliferation of vascular endothelial cells, reducing tumor microvessel density, and inhibiting tumor angiogenesis[11-13]. With the announcement of the results of phase I and phase II clinical trials, the China Food and Drug Administration (CFDA) approved apatinib as the third-line treatment for advanced gastric cancer or adenocarcinoma of the gastroesophageal junction in October 2014.

In this review, we summarize the structure, mechanism and pharmacokinetic characteristics of apatinib, overview the current data of apatinib in clinical studies, and propose future development directions of HCC.

STRUCTURE AND MECHANISM
Angiogenesis plays an important role in the occurrence and development of tumors[13]. Vascular endothelial growth factor (VEGF) and its receptor VEGFR have been thought to play a central role in angiogenesis and tumor growth[13,14]. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PLGF). Similarly, there are three subtypes of receptor family, including VEGFR-1, VEGFR-2, and VEGFR-3[15]. The combination of VEGF-A and VEGFR-2 is considered to be mainly involved in the generation of blood vessels in solid tumors[16-18]. VEGF-A binds to the Ig-like domains 2 and 3 of VEGFR-2 to dimerize the receptor, which in turn causes the tyrosine kinase of receptor to undergo autophosphorylation[13] (Figure 1).

Subsequently, several different molecular pathways are activated simultaneously: The RAF/MEK/ERK pathway promotes endothelial cell proliferation and survival; the p38-MAPK pathway increases the migration and invasion of endothelial cells, and enhances chemotactic and homing of bone marrow-derived vascular precursor cells; and the PI3K/AKT/mTOR pathway improves endothelial cell survival and vascular permeability[14,15,18,21].

Apatinib mesylate is a derivative of valatinib. Its predecessor is YN968D11 (N-[4-(1-cyano-cyclopentyl) phenyl]-2-(4-pyridylmethyl) amino-3-pyridine carboxamide
Figure 1  Schematic illustration of the mechanism of apatinib as an inhibitor of vascular endothelial growth factor receptor 2. VEGFR2: Vascular endothelial growth factor receptor 2.

mesylate). It highly specifically binds to the intracellular ATP binding site of VEGFR-2, preventing receptor phosphorylation. Apatinib has a strong affinity for VEGFR2 (IC$_{50}$ = 2), which is ten times that of other anti-angiogenic drugs such as sorafenib (IC$_{50}$ = 90)\cite{8,9,22,23}.

PHARMACOKINETICS

The pharmacokinetic analysis showed that the time to maximum plasma concentration level after administration was about 3-4 h with an average half-life of 9 h\cite{9}. There are many main pathways of apatinib biotransformation, in which M1-1 is the main metabolite and shows the strongest inhibitory effect on VEGFR-2, and it is most closely related to the anti-angiogenic effect of apatinib. In contrast, M9-2 has no obvious inhibitory effect on the above enzymes. The oxidative metabolites of apatinib are mainly formed in the liver in a NADPH-dependent manner. The process is mainly mediated by the CYP3A4/5 enzyme, followed by CYP2D6, CYP2C9, and CYP2E1. After 96 h of oral apatinib, drug excretion rate was 76.8%, including 69.8% in stool and 7.0% in urine\cite{24}.

PRECLINICAL STUDIES

In vitro experiments

Apatinib can effectively inhibit the activity of VEGFR-2 kinase and block its downstream signaling by specifically competing for the ATP binding site in the cell\cite{8}. Apatinib also inhibits the proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVEC), blocking the germination of rat aortic rings\cite{8,25}.

In HCC, apatinib can induce cell cycle arrest at the G2/M phase, promoting apoptosis of HCC cells in vitro, and its inhibitory effect is related to the expression level of VEGFR\cite{26}. Li et al\cite{27} have found that apatinib promotes tumor cell apoptosis
and inhibits metastasis, which may be related to the down-regulation of PDGFR-α, IGF-IR, and AKT phosphorylation levels. Similar results have been observed in SMMC-7721 cells, in which apatinib promoted apoptosis by inhibiting the phosphorylation level of PI3K/AKT[36]. In pancreatic cancer, apatinib promotes apoptosis of pancreatic cells by down-regulating hypoxia inducible factor-1α (HIF-1α) and increasing reactive oxygen levels[37]. In thyroid cancer, apatinib inhibits the expression of angioptitin through tumor cell AKT/GSK3β/ANG pathway, thereby inhibiting tumor angiogenesis[38]. Apatinib inhibits cell invasion and migration by inhibiting the RET/SRC signaling pathway, suggesting a potential role in treating KIF5B-RET-driven tumors[39]. Apatinib can also promote the apoptosis of tumor cells of extrahepatic bile duct cancer[40], esophageal cancer[41], colon cancer[42], osteosarcoma and glioma[43], and B and T cell acute lymphoblastic leukemia[44].

In vivo experiments

In an immunodeficiency mouse xenograft model of HCC, apatinib was administered orally three times a week, and the inhibition rate of tumor growth was 71% after 30 d, and no significant weight loss or treatment-related death was observed[45]. Liang et al[46] evaluated the therapeutic effect of apatinib and sorafenib in HCC by multimodal molecular imaging. The results showed that apatinib inhibits the growth and angiogenesis of HCC, which is equivalent to sorafenib but has fewer side effects[47]. Apatinib can also cause metabolomics changes. After apatinib treatment, 3-hydroxybutyric acid (3-HB) is significantly increased in serum, tumor, and the liver, which aids antitumor effect of apatinib[48].

Apatinib alone or in combination with chemotherapeutics can effectively inhibit a variety of established human tumor xenograft models with less toxicity. The combination of apatinib with docetaxel and Adriamycin significantly inhibits the growth of transplanted lung cancer, which is significantly different from the apatinib group and the chemotherapy drug group. In addition, the combination of apatinib with oxaliplatin and fluorouracil also showed a significant inhibitory effect in colon cancer[49]. Tong et al[50] selected a subset of K562 leukemia cells with higher doxorubicin resistance as the object of observation. The experimental results showed that apatinib could significantly reduce the IC50 value of doxorubicin in this subgroup of cells and significantly increase the sensitivity to chemotherapy drugs. It was also confirmed in a tumor xenograft model that apatinib could reverse ABCB1 and ABCG2-mediated multidrug resistance (MDR) by directly inhibiting ABCB1 and ABCG2 function, leading to the rise of intracellular concentrations of chemotherapeutic drugs. The reversal of MDR further supports the potential role of combining apatinib with other conventional anticancer drugs in overcoming clinical resistance[51].

**CLINICAL RESEARCH OF ADVANCED HCC**

Qin et al[39] reported a prospective, randomized, open label, nationwide, multicenter, phase II clinical trial of apatinib as second-line therapy for advanced HCC. The primary endpoint of the study was time to disease progression (TTP). The secondary endpoints included OS, ORR, disease control rate (DCR), quality of life, and serum alpha-fetoprotein (AFP) levels. A total of 121 patients with advanced HCC were enrolled and randomly assigned 1:1 to the 850 mg dose group and the 750 mg dose group. The results confirmed that the clinical efficacy of apatinib (850 mg and 750 mg) in different dose groups was basically the same for advanced HCC with initial treatment and good basic conditions: mTTP and mOS were not significantly different between the two groups (4.2 mo vs 3.3 mo, P > 0.05; 9.7 mo vs 9.8 mo, P > 0.05). The DCRs of the two groups were 48.6% and 37.3% (P > 0.05), and the ORRs were 8.6% and 0 (P > 0.05), respectively. The incidence of adverse events was also similar between these two groups. In terms of safety, the drug-related toxicities in the 850 mg dose group were more than those in the 750 mg dose group, but the differences were not statistically significant, including hand-foot skin reaction (HFSR), elevated aminotransferase, and elevated bilirubin. Grade 3 and above drug-related side effects included hypertension, proteinuria, HFSR, fatigue, and peripheral blood cell reduction. Considering that most patients with liver cancer have basic liver diseases, they recommended that 750 mg qd as dose for subsequent studies.

Kong et al[52] retrospectively evaluated the efficacy and safety of apatinib in 22 patients with advanced HCC who were resistant to sorafenib or could not afford sorafenib. Apatinib was administered continuously at 500 mg/d or 250 mg/d with clinical emphasis on TTP, OS, and safety. Until the last follow-up, the median disease
progression time for these 22 patients was 10.4 mo, and 50% of patients survived longer than 11.4 mo. The percentages of patients achieving complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 0%, 40.9%, 40.9%, and 18.2%, respectively, and the ORR and DCR were 40.9% and 81.8%, respectively. At the same time, 14 of the 22 cases had decreased alpha-fetoprotein levels, of which seven had fallen by half or more. Adverse events mainly included proteinuria (81.8%), diarrhea (77.3%), hypertension (63.6%), fatigue (59.1%), hoarseness (54.5%), and nausea (50%). Grade 3 or 4 drug-related adverse events mainly included hypertension (27.3%), HFSR (13.6%), and thrombocytopenia (9.1%). In view of the side effects of advanced patients and the high-dose treatment, patients receiving low-dose treatment (250 mg/d) had fewer and less adverse events and achieved good responses.

A prospective study by Yu et al[43] evaluated the efficacy and safety of apatinib in advanced HCC. A total of 31 patients participated in the study, including four in the intermediate stage and 27 in the advanced stage. The dose was 500 mg/d. According to the first follow-up CT and MRI after 6 wk of treatment, the numbers of patients achieving PR, SD, and PD in 31 patients were 10 (32.3%), 15 (48.4%), and 6 (19.4%). The ORR and DCR were 32.3% and 80.7% respectively. The mPFS was 4.8 mo, and the 6- and 12-mo survival rates were 73.8% and 55.4% respectively. The most common grade 3 adverse effects were hypertension (48.4%), thrombocytopenia (6.5%), and an increase in total bilirubin or transaminase (6.5%). By adjusting drug dosage and symptomatic treatment, all toxic reactions could be controlled.

Liu et al[41] retrospectively reviewed the efficacy and safety of apatinib in the treatment of unresectable or recurrent HCC. A total of 32 patients with HCC or intrahepatic bile duct cancer were included in the study[41]. No CR occurred, PR, SD, and PD were observed in 5 (16%), 14 (44%), and 13 (41%) patients, respectively, and DCR was 60%. The mPFS for HCC was 5 mo, and the mPFS for intrahepatic cholangiocarcinoma was 3 mo. The mOS for HCC and bile duct carcinoma were 13 mo and 5 mo, respectively. The most common adverse effects were proteinuria (31%), hypertension (28%), and liver dysfunction (13%).

Zhang et al[44] evaluated the efficacy and safety of apatinib for sorafenib refractory advanced hepatitis B virus-associated HCC. A total of 43 patients were retrospectively analyzed[44]. ORR and DCR were 25.6% and 67.4%, respectively. mPFS and mOS were 3 mo and 8 mo, respectively. The 1-year and 2-year survival rates were 34.9% and 9.3%, respectively. The most common toxicities were weight loss, HFSR, and hypertension.

Apatinib shows a therapeutic effect on advanced HCC with lung metastasis[45]. In a retrospective and multicenter study, 61 patients with advanced HCC were enrolled in the study, including 41 patients with lung metastases, three with multiple organ metastases, and 20 with no pulmonary metastases. The main focus was on metastasis specificity and PFS. All patients had a median PFS of 3.37 mo and an ORR of 11.6%. The median mPFS of 41 patients with pulmonary metastases was 5 mo, and the mPFS for intrahepatic bile duct carcinoma was 3 mo. The mOS for HCC and bile duct carcinoma were 13 mo and 5 mo, respectively. The most common adverse effects were proteinuria (31%), hypertension (28%), and liver dysfunction (13%).

In a series of clinical studies of apatinib, common adverse events include hematological toxicity (leukopenia, granulocytopenia, and thrombocytopenia) and non-hematological toxicity (hypertension, proteinuria, HFSR, etc.). Among the common important adverse events are hypertension, proteinuria, and HFSR.

In the phase I study of apatinib, the overall incidence of hypertension reached 69.5%, of which grade 3 to 4 reached 6.5%. Hypertension is the most common adverse reaction of anti-angiogenic drugs, especially VEGF/VEGFR inhibitors. Current research suggests that reduction of nitric oxide (NO) and increase of endothelin (ET) are the main causes of hypertension in anti-VEGF treatment[46,47]. Both methods can cause vasodilation dysfunction and strengthen systolic function. In addition, abnormal blood vessel density and reduced capillaries are also the cause of hypertension[48]. In the current treatment plan, besides reducing the drug dose, another effective treatment is the use of antihypertensive drugs.

The overall incidence of proteinuria in the phase I study was 34.8%, and the incidence of grade 3 to 4 was 13%. The occurrence of proteinuria is related to the inhibition of VEGF signaling by apatinib, whereas adequate VEGF is needed to maintain the integrity of glomerular structure and function. In animal experiments, podocyte specific VEGF gene knockout can cause structural and functional changes, which in turn affects glomerular filtration rate and causes proteinuria[49]. Although the
The overall incidence of HFSR in phase I clinical studies was 45.6%, and the incidence in grade 3 to 4 was 13%, which can be alleviated by reducing the dose of the drug. Its mechanism is unknown. Possible reasons include: Decreased renewal and dysfunction of endothelial cells; damage to sweat ductal epithelial cells due to inhibition of PDGF and c-Kit; keratinocyte dysfunction due to c-Kit inhibition; and broken balance between vascular and epidermal damage\(^\text{[50]}\)\(^\text{[51]}\).

In addition to the common adverse events mentioned above, other adverse events include bleeding, fatigue, diarrhea, infection, dyspnea, hoarseness, skin albinism, and rash. However, most of these events are mild and controllable, and can be relieved with supportive treatment. Remarkably, clinical trials have shown that adverse events caused by apatinib are often associated with better efficacy and longer survival benefits\(^\text{[52]}\).

### THE FUTURE OF APATINIB IN HCC

The combination of apatinib with other treatments has yielded interesting results in advanced HCC. In the combination with trans-artery chemo-embolization (TACE), Zhu et al\(^\text{[53]}\) reported that after 9 mo of TACE combined with apatinib for advanced HCC, DCR and ORR in the TACE group were 81.82% and 36.36%, and they were 95.45% and 63.64% in the TACE plus apatinib group. The PFS was 11.15 and 16.5 mo, respectively\(^\text{[53]}\). DCR, ORR, and PFS were significantly improved. There was no significant difference in the incidence of adverse events after embolization between the two groups of patients. However, the incidence of hypertension, HFSR, and proteinuria in the combined group was significantly higher (\(P < 0.05\)). Adverse effects were alleviated after symptomatic treatment.

Xu et al\(^\text{[54]}\) studied the effect of carrelizumab (PD-1 mAb, SHR-1210) and apatinib in the treatment of advanced HCC, gastric cancer, and esophagogastric junction cancer in a phase I clinical study\(^\text{[54]}\). Of the 16 evaluable HCC patients, eight achieved PR, in whom one was in the apatinib 125 mg cohort and seven received apatinib 250 mg. ORR and DCR were 50.0% and 93.8%, respectively. Patients receiving apatinib had a 6-mo PFS rate of 51.3% and a 9-mo PFS rate of 41%. A phase III study on the combined use of the two drugs is underway (NCT02329860).

### CONCLUSION

Apatinib, as a new type of small molecule tyrosine kinase inhibitor, shows high selective affinity for VEGFR-2, blocking its downstream signal transduction. Although there is no sufficient evidence, from the primary research and exploration, apatinib may have potential advantages, such as better ORR, survival benefits, and less toxic and side effects, which is still waiting for further research and confirmation. Combined therapy shows a prominent role by working through different mechanisms and will hold an important position in the future\(^\text{[55]}\). Apatinib, as an alternative targeted drug, will be likely to have a promising effect in combination therapy. A number of clinical trials of combination therapy including apatinib are currently underway (NCT03793725, NCT03839550, NCT03463876, and NCT03764293). Current research still has certain limitations. Most of the studies are small in size. The mechanisms need further exploration to ensure a higher level of evidence. With the development of basic and clinical research, apatinib alone or in combination with other therapy may benefit more patients with HCC.

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