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INVITED REVIEW ARTICLE

Clinical trials of antiangiogenic therapy for hepatocellular carcinoma

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Abstract Angiogenesis is a promising therapeutic target to inhibit tumor growth. This review summarizes data from clinical trials of antiangiogenic agents in hepatocellular carcinoma. A systematic search of PubMed was performed to identify clinical trials of specific antiangiogenic agents in hepatocellular carcinoma treatment, particularly phase III trials involving treatment guidelines for advanced hepatocellular carcinoma. Sorafenib is the only systemic drug approved for the treatment of advanced hepatocellular carcinoma. Two large-scale, randomized phase III trials using sorafenib involving patients with unresectable HCC showed a significant survival benefit compared with placebo control groups. However, subsequent phase III trials of antiangiogenic agents in hepatocellular carcinoma have failed to improve survival compared with standard treatment protocols using sorafenib. The efficacy of antiangiogenic agents in combination with other drugs, transarterial chemoembolization, and surgical resection is currently being investigated. Future research is expected to optimize antiangiogenic therapies in combination with standard treatment with sorafenib.

Keywords Angiogenesis · Antiangiogenic therapy · Hepatocellular carcinoma · Sorafenib

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Introduction

Hepatectomy and liver transplantation has been accepted as a curative modality for patients with hepatocellular carcinoma (HCC) [1, 2]. On the other hand, there have been attempts to develop alternative or combination treatments in order to improve the overall survival (OS) of patients with advanced HCC, including chemotherapy, molecular target therapy, gene therapy, or immunotherapy [3, 4]. Hypervascularization is a major characteristic of HCC (Fig. 1). Antiangiogenic treatments, which inhibit blood vessel formation, are reportedly highly effective for treating HCC. However, the efficacy and safety of antiangiogenic therapies remain controversial. In the present work, we review recent developments in antiangiogenic therapies for advanced HCC, particularly the outcomes of randomized phase III trials (Table 1).

Multikinase inhibitors

Several small-molecule, orally available receptor tyrosine kinase inhibitors show an antiangiogenic ability to inhibit vascular endothelial growth factor (VEGF) and other kinases, and have undergone extensive evaluation or are currently being tested in clinical trials of varying stages for the treatment of advanced HCC. These agents include sorafenib, lenvatinib, sunitinib, cabozantinib, brivanib, and linifanib.

Sorafenib

Sorafenib is a multiple-kinase inhibitor that suppresses proliferation and angiogenesis by inhibiting the activities

of RAF kinase and the receptors for VEGF [5]. Two large-scale, placebo-controlled, randomized, comparative studies involving patients with unresectable HCC (the SHARP and Asia–Pacific studies) showed an increased disease control rate, a significant prolongation of the survival period, and a 30 % decrease in the risk of death [6, 7]. The SHARP trial reported better median OS without significant drug toxicity in sorafenib-treated patients [10.7 months in the sorafenib group vs 7.9 months in the placebo group; hazard ratio (HR) = 0.69; 95 % confidence interval (CI) 0.55–0.87, $P < 0.001$] [6]. Subsequent subgroup analyses revealed that sorafenib consistently improved the median OS and median time to tumor progression (TTP) in comparison with the control group, irrespective of disease etiology, baseline tumor extent, tumor stage, prior therapy, and performance status. In particular, patients with macrovascular invasion who were treated with sorafenib demonstrated a longer median OS (8.1 vs 4.9 months) and TTP (4.1 vs 2.7 months) [8]. Currently, sorafenib is the only systemic agent demonstrated to produce a significant improvement in both OS and progression-free survival (PFS) in patients with advanced HCC. Additionally, the guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend sorafenib as a first-line treatment in patients with advanced HCC [9, 10]. Peng et al. conducted a meta-analysis of seven randomized controlled trials assessing the effect of sorafenib in a total of 3807 patients with advanced HCC [11]. Pooled estimates showed that sorafenib improved OS (HR = 0.74, 95 % CI 0.61–0.90; $P = 0.002$) or TTP outcomes (HR = 0.69, 95 % CI 0.55–0.86; $P = 0.001$).

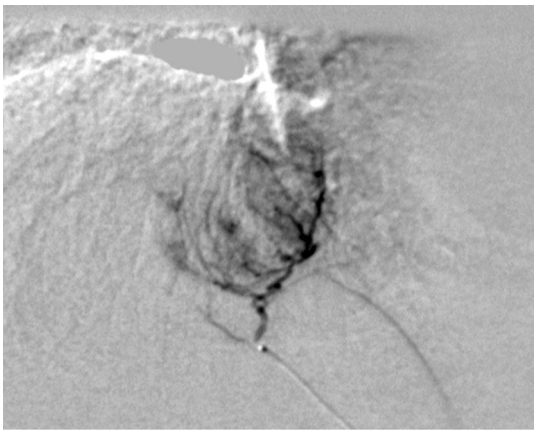

Fig. 1 Typical hepatic arterial angiography of HCC with high vascularity

In clinical practice, however, unsatisfactorily low tumor regression (around 2–3 %) and median OS (usually less than 1 year) are observed in patients receiving sorafenib. Furthermore, substantial evidence of primary and acquired

Table 1 Summary of phase III clinical trials of antiangiogenic therapy for HCC

No.	Year	Trial	Line	Design	Patients	Median OS (months)	HR (95 % CI)	*p* value	References
1	2008	SHARP	1st	Sorafenib	299	10.7	0.69 (0.55–0.87)	<0.001	[5]
				Placebo	303	7.9			
2	2009	Asian–Pacific	1st	Sorafenib	150	6.5	0.68 (0.50–0.93)	0.014	[6]
				Placebo	76	4.2			
3	2015	SEARCH	1st	Erlotinib + Sorafenib	362	9.5	0.93 (0.78–1.10)	0.408	[11]
				Placebo + Sorafenib	358	8.5			
4	2013	SUN1170	1st	Sunitinib	530	7.9	1.30 (1.13–1.50)	0.0014	[22]
				Sorafenib	544	10.2			
5	2013	BRISK-FL	1st	Brivanib	577	9.5	1.06 (0.93–1.22)	0.3730	[30]
				Sorafenib	578	9.9			
6	2015	NCT01009593	1st	Linifanib	514	9.1	1.05 (0.90–1.22)	ND	[34]
				Sorafenib	521	9.8			
7	2013	BRISK-PS	2nd	Brivanib	263	9.4	0.89 (0.69–1.15)	0.3307	[31]
				Placebo	132	8.2			
8	2015	REACH	2nd	Ramucirumab	283	9.2	0.87 (0.72–1.05)	0.14	[37]
				Placebo	282	7.6			
						Median RFS (months)			
9	2015	STORM	Adjuvant	Sorafenib	556	33.3	0.94 (0.78–1.13)	0.26	[12]
				Placebo	558	33.7			

HCC hepatocellular carcinoma, *HR* hazard ratio, *ND* not described, *OS* overall survival, *RFS* recurrence-free survival

resistance to sorafenib has also been reported. To improve the outcome of sorafenib treatment, efficacy in combination with other agents, transarterial chemoembolization, and surgical resection are currently being investigated. In a phase III clinical trial (SEARCH) of sorafenib in combination with erlotinib for advanced HCC, median OS was shown to be similar in the sorafenib/erlotinib and sorafenib/placebo groups (9.5 vs 8.5 months), as was median TTP (3.2 vs 4.0 months) [12]. There was no significant difference in overall response rate between the two groups (6.6 vs 3.9 %). Therefore, adding erlotinib to sorafenib did not improve survival in patients with advanced HCC. Furthermore, a phase III study (STORM) of adjuvant use of sorafenib in HCC patients after curative resection or ablation therapy reported that sorafenib did not significantly affect recurrence-free survival, time to recurrence, or OS after curative treatment [13]. These findings suggest an urgent need to optimize or develop an "add-on" strategy to further build on the early successes of sorafenib therapy.

Lenvatinib

Lenvatinib is a multitargeted tyrosine kinase inhibitor with potent antiangiogenic effects, and has recently been approved for use in differentiated thyroid cancer [14]. Gu et al. established patient-derived xenograft models that faithfully recapitulated the genetic and phenotypic features of HCC and demonstrated that, in models expressing high levels of fibroblast growth factor (FGF) receptor 1, the FGFR1 inhibitor lenvatinib showed greater efficacy than sorafenib [15]. In the clinical setting, lenvatinib has also shown highly promising response data (median OS of 18.7 months; median TTP of 7.4 months) in phase I/II clinical trials in advanced HCC with Child–Pugh class A liver function [16]. Results from the recently completed pivotal phase III REFLECT trial comparing lenvatinib with sorafenib will determine whether lenvatinib represents a breakthrough in the current crisis affecting HCC drug development [17].

Sunitinib

Sunitinib is an oral multitargeted receptor tyrosine kinase inhibitor that targets VEGF receptors 1, 2 and 3, and other receptor tyrosine kinases implicated in angiogenesis [18]. Four separate phase II studies evaluated different dosing schedules of sunitinib as a treatment for advanced HCC [19–22]. These phase II trials showed favorable results in terms of antitumor activity against advanced HCC. In 2013, an open-label phase III trial was carried out on a total of 1074 patients randomized either to sunitinib (530 patients) or sorafenib (544 patients) [23]. Median OS was 7.9 and 10.2 months in the sunitinib and sorafenib groups ($P = 0.0014$), respectively, although median PFS and TTP were not significantly different between the two groups. In terms of safety, more adverse effects were reported in the sunitinib group, especially thrombocytopenia (29.7 %) and neutropenia (25.7 %). However, more instances of hand-foot syndrome (21.2 %) were observed in the sorafenib group. This study showed that sunitinib had no benefit over sorafenib as a first-line therapy for advanced HCC.

Cabozantinib

Cabozantinib, approved in 2012 by the United States Food and Drug Administration [24], is a small-molecule tyrosine kinase inhibitor with potent activity towards VEGF (VEGFR-2), MET, and RET (rearranged during transfection), all of which are implicated in tumor pathogenesis, leading to the inhibition of tumor angiogenesis [25]. In a phase II study on nine solid tumor types, treatment with cabozantinib was evaluated on 41 patients with advanced HCC who were administered 100 mg of the drug orally for 12 weeks. The observed disease control rate after 12 weeks was found to be 68 %, and 78 % of the patients with or without prior sorafenib treatment showed tumor regression. Thirty-two patients of the 36 showed stable disease, two showed a confirmed partial response, and median PFS was calculated to be 4.2 months for both sorafenib-pretreated and sorafenib-naïve patients [26]. A phase III, randomized, double-blind, controlled trial is ongoing to compare the efficacy of cabozantinib with placebo as the second-line treatment modality for advanced HCC patients who have received prior sorafenib (NCT01908426) [27]. A total of 760 subjects are planned for recruitment into this trial; the primary endpoint is OS, and the secondary endpoints include PFS and objective response rate.

Brivanib

Brivanib, the first oral selective dual inhibitor of FGF and VEGF signaling, is formulated as an orally administered L-alanine ester prodrug, brivanib alaninate [28]. Brivanib has demonstrated antitumor activity in xenograft HCC models expressing FGF receptors [29]. Thus, targeting both VEGF and FGF signaling pathways may provide clinical benefits to HCC patients. A phase II study of brivanib as first-line therapy in 55 patients with advanced HCC reported a 6-month PFS rate of 18.2 % and median PFS of 2.7 months. One patient achieved a complete response and three achieved a partial response. Twenty-two patients had stable disease, and median OS was 10 months [30]. Two phase III, randomized, double-blind, controlled trials have also been conducted: the BRISK-FL study of brivanib vs sorafenib as first-line therapy in patients with unresectable, advanced HCC [31], and the BRISK-PS study of brivanib

in patients with advanced HCC who were intolerant of sorafenib or for whom sorafenib failed [32]. The BRISK-FL study failed to meet the primary endpoint of improving OS (brivanib 9.5 months, sorafenib 9.9 months) that was required to show noninferiority. The BRISK-PS trial also failed to meet the primary endpoint of improving OS statistically (9.4 vs 8.2 months).

Linifanib

Linifanib is a novel ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases that lacks significant activity against representative cytosolic tyrosine kinases and serine/threonine kinases [33]. In an open-label phase II trial, linifanib demonstrated significant clinical activity as monotherapy in patients with advanced HCC, with an independently assessed median TTP of 5.4 months and a median OS of 9.7 months [34]. A randomized phase III trial to evaluate the efficacy and tolerability of linifanib as first-line therapy vs sorafenib (NCT01009593) was conducted in 1035 advanced HCC patients who had received no prior systemic therapy. This trial failed to meet its primary endpoint, showing similar OSs with linifanib and sorafenib [9.1 months (95 % CI 8.1–10.2) for linifanib vs 9.8 months (95 % CI 8.3–11.0; HR, 1.046; 95 % CI 0.896–1.221) for sorafenib] [35].

Monoclonal antibodies

Monoclonal antibodies that specifically target malignant cells or tumor growth are now available for cancer therapy. Bevacizumab is a monoclonal antibody against tumor angiogenesis, and is widely used to treat solid cancers, particularly colorectal cancer, in combination with chemotherapy.

Ramucirumab

Ramucirumab is a recombinant IgG1 monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity, preventing binding of VEGF ligands and receptor activation [36]. Results of phase II studies showed antitumor activity of ramucirumab as first-line treatment for HCC [37]. A randomized, double-blind, phase III trial (REACH study) of ramucirumab as second-line treatment was performed in patients with advanced HCC following first-line therapy with sorafenib [38]. In this study, 565 patients were enrolled, 283 of whom were assigned to ramucirumab and 282 to placebo. The median OS for the ramucirumab group (9.2 months) was not significantly different from that of the placebo group (7.6 months). Second-line treatment with ramucirumab did not significantly improve survival over placebo in patients with advanced HCC.

Bevacizumab

Bevacizumab is an anti-VEGF recombinant humanized monoclonal IgG1 antibody which is widely used for the treatment of metastatic colorectal cancer [39]. Bevacizumab has shown promising activity in a single-arm phase II trial in advanced HCC patients [40]. In this study, 13 % of patients showed a partial response and 65 % reported PFS at 6 months. Adverse events were mild, except for grade 3–4 hemorrhage occurring in 11 % of patients. Bevacizumab has been used for advanced HCC in combination with chemotherapy (including gemcitabine, oxaliplatin, and/or capecitabine) rather than as monotherapy [41–43]. Zhu et al. showed that combining bevacizumab with gemcitabine and oxaliplatin resulted in a 20 % overall response rate in evaluable patients and stable disease in 27 % of patients. Median OS was 9.6 months and median PFS was 5.3 months [41]. Bevacizumab in combination with capecitabine resulted in an overall response rate of 9 % and a disease-control rate of 52 % [43].

Conclusion and future directions

At present, the global standard of care for advanced HCC patients is sorafenib monotherapy. As described in this review, none of the antiangiogenic drugs or combinations tested to date have improved survival compared with sorafenib monotherapy. Phase III trials of sunitinib, linifanib, and brivanib as first-line treatment, as well as data from second-line trials of brivanib, have been negative. A phase III trial using the monoclonal antibody ramucirumab also failed to produce a new effective therapy for the second-line treatment of HCC.

Significant efforts should be made to advance knowledge of the molecular mechanisms of HCC initiation and progression. In particular, the target of antiangiogenic therapy should be redirected from human normal endothelial cells to tumor endothelial cells, as described in the paired review article. Such endeavors may result in improved treatment options that would increase survival in patients with advanced HCC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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