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REVIEW

Antiangiogenic treatment in hepatocellular carcinoma: the balance of efficacy and safety

Martin-Walter Welker
Joerg Trojan

Medizinische Klinik 1,
Universitätsklinikum Frankfurt,
Germany

Abstract: Hepatocellular carcinoma (HCC) is a severe complication of advanced liver disease with a worldwide incidence of more than 600,000 patients per year. Liver function, clinical performance status, and tumor size are considered in the Barcelona Clinic Liver Cancer (BCLC) system. While curative treatment options are available for early stages, most patients present with intermediate- or advanced-stage HCC, burdened with a poor prognosis, substantially influenced by the degree of liver-function impairment. Hypervascularization is a major characteristic of HCC, and antiangiogenic treatments are the basis of treatment in noncurative stages, including interventional and pharmacological treatments. Currently, the tyrosine-kinase inhibitor sorafenib is still the only approved drug for HCC. Further improvements in survival in patients with intermediate- and advanced-stage HCC may be anticipated by both multimodal approaches, such as combination of interventional and systemic treatments, and new systemic treatment options. Until now, the Phase III development of other tyrosine-kinase inhibitors in patients with advanced HCC has failed due to minor efficacy and/or increased toxicity compared to sorafenib. However, promising Phase II data have been reported with MET inhibitors in this hard-to-treat population. This review gives a critical overview of antiangiogenic drugs and strategies in intermediate- and advanced-stage HCC, with a special focus on safety.

Keywords: HCC, sorafenib, antiangiogenesis, TACE, MET

Introduction

The worldwide incidence of hepatocellular carcinoma (HCC) exceeds 600,000 patients per year, and is still rising.[1] An important characteristic of HCC is the predominant occurrence in liver cirrhosis and advanced chronic liver disease.[1] This explains why overall prognosis remains poor, as survival may depend on impaired liver function rather than tumor progression in some patients, and therapeutic options often are limited by potential hepatotoxicity.[1,2]

The Barcelona Clinic Liver Cancer (BCLC) therapeutic algorithm takes this into account by combining tumor stage, clinical performance status, and liver function to stratify prognosis and treatment.[3,4] Early stages (BCLC 0 and BCLC A) are characterized by limited tumor size and preserved liver function, while intermediate- (BCLC B), advanced- (BCLC C), and end-stage (BCLCD) cancer are defined by extended tumor size and decreased liver function. Consequently, surgical (resection or transplantation) or percutaneous thermal therapies (radiofrequency or microwave ablation) are mainly considered suitable for the early stage, while interventional therapies (transarterial chemo- or radioembolization) are applied in patients with intermediate-stage HCC. Systemic treatment with the tyrosine-kinase inhibitor sorafenib is considered the

Correspondence: Joerg Trojan
Medizinische Klinik 1,
Universitätsklinikum Frankfurt,
Theodor-Stern-Kai 7, Frankfurt
60590, Germany
Tel +49 69 6301 7860
Fax +49 69 6301 6448
Email trojan@em.uni-frankfurt.de

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treatment of choice for patients with advanced-stage HCC. Patients with BCLC stage D do not benefit from cancer treatment, and thus are being considered for best supportive care only. Thus, recent strategies have focused on the establishment of new drugs for patients with advanced-stage HCC. Moreover, selected current trials focus on adjuvant pharmacological treatment options in early stage HCC or combination of interventional therapies and sorafenib in intermediate-stage HCC.

The development of efficient new drugs in HCC is challenged by the need for a safety profile, defined by low or absent hepatotoxicity and nephrotoxicity. Moreover, putative accumulation of the agent and its metabolites in patients with impaired liver and/or kidney function has to be taken into account and must be avoided.

Theoretically, HCC should be prone to inhibition of angiogenesis because it is a highly vascular tumor, and hypervascularization is an essential characteristic of HCC, closely linked to carcinogenesis and progression.[5–7] Indeed, antiangiogenic treatment of HCC, either by mechanical destruction of arterial tumor vessels after transarterial chemoembolization (TACE) or by pharmacological inhibition with the dual-kinase inhibitor sorafenib, which is still the only systemic agent approved for HCC, is the current basis of noncurative approaches in HCC.[8–12] So far, antiangiogenic tyrosine-kinase inhibitors other than sorafenib have failed in randomized placebo-controlled pivotal trials, due to either minor efficacy or unacceptable toxicity profiles. This review gives a critical overview of established antiangiogenic drugs and those currently being developed, and strategies with special focus on safety in intermediate- and advanced-stage HCC.

Angiogenesis in liver cirrhosis and HCC

Angiogenesis is closely related to chronic hepatitis and hepatic fibrogenesis, which in turn may lead to liver cirrhosis and HCC. The vascular endothelial growth-factor (VEGF) pathway was identified as the major driver in tumor angiogenesis. However, activation and/or upregulation of abundant proangiogenic signaling pathways may lead to resistance to VEGF-based antiangiogenic therapy, reinducing tumor angiogenesis and subsequently resulting in tumor progression.[5] VEGF is crucially involved in angiogenesis, as well as in fibrogenesis in chronic liver disease, but other cytokines, growth factors, and metalloproteinases are additionally involved in these processes.[13] HCC nodules larger than 2 cm typically show early arterial enhancement, a surrogate of hypervascularization, which is pathognomonic for HCC.[6,7] In patients with HCC, higher VEGF serum levels were associated with poor outcome in the majority of but not all studies addressing this issue.[14–19] Moreover, increased expression of angiopoietin 1/2 messenger RNA in tumor tissue, another proangiogenic factor, has been reported in patients with HCC.[20] Therefore, it may be concluded that angiogenesis in HCC is a complex process and most likely heterogeneous.

Sorafenib in advanced hepatocellular carcinoma

The proof of concept that pharmacological inhibition of angiogenesis is clinically meaningful in HCC was provided by four clinical trials showing consistently a survival benefit of approximately 3 months in patients with advanced HCC and preserved liver function treated with sorafenib, which is still the only systemic agent approved for advanced HCC.[21–24] Sorafenib is a multikinase inhibitor with activity against VEGF receptor (VEGFR)-2, platelet-derived growth-factor receptor (PDGFR), receptor of the tyrosine kinase c-Kit, rapidly accelerated fibrosarcoma B kinase, and mitogen-activated protein kinase p38 signal-transduction pathways, which seem to be involved in the pathogenesis of HCC.[8] The main effect of sorafenib is disease stabilization, and sorafenib can be used with an acceptable safety profile under daily practice conditions.[25,26] However, adverse effects – mainly fatigue, diarrhea, and hand–foot syndrome – may significantly alter quality of life and may lead to dose reduction of sorafenib.[21–26] Within a recent Phase II study, dose escalation of sorafenib was not superior to best supportive care in patients with advanced HCC and disease progression during sorafenib 400 mg twice daily, while adverse events (diarrhea 80%, weight loss 75%, fatigue 67%, hand–foot skin reaction 49%, abdominal pain 37%, stomatitis 26%) were common.[27]

Antiangiogenic drugs in clinical development

A consequent step of antiangiogenic drug development was to investigate tyrosine-kinase inhibitors with other or additional targets than sorafenib in HCC. Sunitinib, a tyrosine-kinase inhibitor targeting the tyrosine kinase Kit, PDGFR-α and -β, and VEGFR1, -2, and -3, was compared to sorafenib as first-line treatment of advanced HCC in the SUN1170 trial.[28] This trial was terminated early because of a higher rate of drug-related adverse events in the sunitinib arm, including fatal outcomes. Overall survival in patients taking sunitinib was 7.9 months compared to 10.2 months in the sorafenib arm. Linifanib, a selective VEGFR and PDGFR tyrosine-kinase inhibitor, was also investigated in first-line treatment of

advanced HCC compared to sorafenib.[29] Linifanib was less effective than sorafenib, with a median overall survival of 9.1 months compared to 9.8 months in the sorafenib arm. A comparison of overall survival in current head-to-head Phase III studies investigating sorafenib, sunitinib, brivanib, linifanib, and erlotinib is given in Figure 1.

Recently, it was shown that inhibition of the fibroblast growth-factor receptor (FGFR)-4 pathway is involved in HCC development in a mouse model.[30] Brivanib, a selective dual inhibitor of VEGFR and FGFR,[31] was shown to have antitumor activity in patients with advanced HCC in two open-label Phase II studies.[32,33] Unfortunately, brivanib was not superior compared to placebo in patients after sorafenib-treatment failure or intolerance to sorafenib in a Phase III study.[34] In another Phase III trial comparing brivanib and sorafenib as first-line treatment in advanced HCC, brivanib failed to prove noninferiority in comparison to sorafenib. Moreover, serious adverse events were common in both the brivanib (59%) and sorafenib (52%) treatment arms.[35] Therefore, the development of brivanib in HCC was stopped. Of note, the combination of sorafenib and the EGFR inhibitor erlotinib was not superior to sorafenib alone in terms of progression-free or overall survival.[1] Moreover, the toxicity profile of this combination was worse than that of sorafenib alone. The results of recent clinical trials in advanced HCC are summarized in Table 1.

Toxic effects of antiangiogenic therapy in HCC

Based on the clinical trial experience of the last few years with antiangiogenic agents in HCC, certain "class" toxicity profiles have emerged. In HCC, as in other malignancies, these include hypertension, bleeding, thromboembolic events, and proteinuria. Some toxic effects are more specific for tyrosine-kinase inhibitors, eg, hand–foot skin reaction, rash, and diarrhea. In addition, a general problem of antiangiogenic agents in HCC is the risk of worsening liver function, which might result in liver-enzyme elevation and fatigue, and more importantly in jaundice, hepatic encephalopathy, and ascites.

With sorafenib, these side effects are manageable.[21–24] However, especially in "dirty" kinase inhibitors, such as sunitinib, liver-specific toxicity seems to be even more prominent.[28] Therefore, a goal of future development of antiangiogenic agents in HCC is a manageable side-effect profile with a low incidence of liver-related toxicity.

Transarterial chemoembolization as antiangiogenic treatment

Hepatic tissue hypoxemia, amongst others, seems to be a relevant trigger for angiogenesis in chronic liver disease via induction of VEGF.[36] TACE was introduced into treatment algorithms for intermediate-stage HCC years before the approval of sorafenib. TACE may lead to reduction of tumor vascularization and viable tumor volume in HCC,[37,38] and response to TACE is higher in patients with lower baseline VEGF serum levels.[39] Increased expression of VEGF after TACE has been reported, and development of satellite HCC nodules adjacent to TACE-treated lesions is a known clinical problem.[40–43] TACE-induced hypoxemia may therefore trigger the expression of angiogenic factors, ultimately resulting in

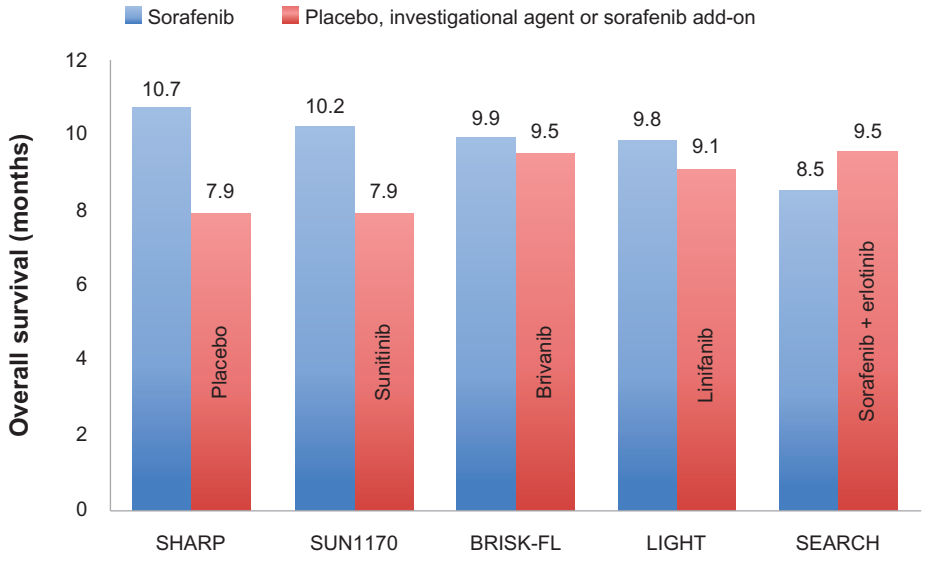

Figure 1 Overall survival in patients with advanced hepatocellular carcinoma treated with sorafenib (all studies, including the pivotal SHARP trial),[21] sunitinib (SUN1170 trial),[28] brivanib (BRISK-FL trial), linifanib, (LIGHT trial),[29] and sorafenib plus erlotinib (SEARCH trial),[135] according to current head-to-head Phase III studies.

Table 1 Efficacy of systemic targeted monotherapy in hepatocellular carcinoma according to current Phase I–III studies

Author	Year	Phase	Investigational drug	n	RR	DCR	PFS/TTP	OS
O'Neil et al[68,a]	2009	II	AZD 6244	16	0	37.5	nr	nr
Schwartz et al[69,b]	2006	II	Bevacizumab	30	6.7	57	nr/6.4	nr
Siegel et al[70,b]	2008	II	Bevacizumab	46	13	65	6.9/nr	12.4
Boige et al[71]	2012	II	Bevacizumab	43	14	42	nr	nr
Kim et al[72]	2012	II	Bortezomib	35	4	37	nr/1.6	6.0
Park et al[33]	2011	II	Brivanib	55	7.2	47.2	2.7	10.0
Finn et al[32]	2012	II	Brivanib	46	4.3	45.7	nr/2.7	9.8
Johnson et al[35]	2012	III	Brivanib	1,155 (577 brivanib)	12	66	nr/4.2	9.9
Llovet et al[34]	2012	III	Brivanib	395 (263 brivanib)	11.5	71.2	nr/4.2	9.4
Gruenwald et al[73]	2007	II	Cetuximab	27	0	44	2.0/1.9	nr
Zhu et al[74]	2007	II	Cetuximab	30	0	17	1.4/nr	9.6
Philip et al[75]	2005	II	Erlotinib	38	9	50	3.2/nr	13.0
Thomas et al[76]	2007	II	Erlotinib	40	0	43	3.1/nr	6.25 (10.75)[c]
Shiah et al[77]	2013	I	Everolimus	39	nr	44.4/71.4[d]	nr	nr
Zhu et al[78]	2011	I/II	Everolimus	25	4	44	3.8/nr	8.4
O'Dwyer et al[79]	2006	II	Gefitinib	31	3	22.5	2.8/nr	6.5
Lin et al[80]	2008	II	Imatinib	15	0	13.3	nr/nr	nr
Bekaii-Saab et al[81]	2009	II	lapatinib	26	0	40	1.9/nr	12.6
Ramanathan et al[82]	2009	II	lapatinib	40	5	35	2.3/nr	6.2
Toh et al[83]	2013	II	linifanib	44	9.1	nr	nr/3.7	9.4
Cainap et al[29]	2013	III	linifanib	1,035 (1:1 randomization)	nr	nr	nr/5.4	9.1
Rizell et al[84]	2008	II	Sirolimus	21	4.8	23.8	nr/nr	6.5
Furuse et al[23]	2008	I	Sorafenib	27	4	83	nr/4.9	15.6
Abou-Alfa et al[22]	2006	II	Sorafenib	137	2.2	33.6	nr/4.2	9.2
Yau et al[24]	2009	II	Sorafenib	51	8	18	3.0/nr	5.0
Llovet et al[21]	2008	III	Sorafenib	602 (299 sorafenib)	2.0	71	nr/5.5	10.7
Cheng et al[85]	2009	III	Sorafenib	226 (150 sorafenib)	3.3	54	nr/2.8	6.5
Kudo et al[86]	2011	III	Sorafenib	458 (229 sorafenib)	nr	nr	nr/5.4[e]	29.7
Hoda et al[87]	2008	II	Sunitinib	23	6	35	nr/nr	nr
Zhu et al[88]	2009	II	Sunitinib	34	2.9	47	3.9/4.1	9.8
Faivre et al[89]	2009	II	Sunitinib	37	2.7	35	3.7/5.3	8.0
Koeberle et al[90]	2010	II	Sunitinib	45	2	40	2.8/2.8	9.3
Wörns et al[91]	2010	II	Sunitinib	11	nr	40	nr/3.2	8.4
Barone et al[92]	2013	II	Sunitinib	34	11.8	44.1	nr/2.8	5.8
Cheng et al[28,a]	2011	III	Sunitinib	1,073 (529 sunitinib)	nr	nr	3.6/4.1	8.1
Pinter et al[93]	2008	I/II	Thalidomide	28	0	7.1	nr	5.1
Santoro et al[94]	2013	I	Tivantinib	21	0	45	nr/3.3	nr
Santoro et al[95]	2013	II	Tivantinib	107 (71 tivantinib)	3	44	1.5/1.6	6.6
Kanai et al[96]	2010	I/II	TSU-68	35	8.6	42.8	nr/2.1	13.1
Hsu et al[97]	2012	II	Vandetanib	90 (67 vandetanib)	0	16.0; 5.3[f]	1.7; 1.1[f]	5.75;5.95[f]

Notes: [a]Trial stopped; [b]overlap of patient cohorts cannot be excluded from information provided; [c]recorded from therapy start (recorded from diagnosis); [d]for weekly and daily treated cohorts, respectively; [e]only patients with advanced HCC and response to TACE were included, and TTP did not differ significantly between sorafenib and placebo; [f]for vandetanib 100 or 300 mg, respectively. For a better comparison of study results, efficacy according to RECIST criteria is given, as some studies used RECIST and some RECIST and modified RECIST criteria.

Adapted from Welker and Trojan.[67]

Abbreviations: DCR, disease-control rate (complete response + partial response + stable disease [%]); OS, overall survival (months) – may differ between studies with respect to start point (start of therapy/diagnosis); PFS/TTP, progression-free survival/time to progression (months); RR, response rate (complete + partial response [%]); nr, not reported; TACE, transcatheter arterial chemoembolization; RECIST, Response Evaluation Criteria in Solid Tumors trial; HCC, hepatocellular carcinoma.

tumor progression.[40–44] These observations form the rationale for combining TACE – or other trans-arterial treatments – with sorafenib, in order to prevent upregulation of VEGF. Several trials using a combination of sorafenib with lipiodol-based TACE, doxorubicin-eluting beads (DEB)-TACE, and selective internal radiation therapy (SIRT) have been reported (Table 2). The combination of sorafenib and TACE seems favorable in a subgroup of patients, but current data are controversial.[45–54] In a recent meta-analysis, the efficacy of DEB-TACE was reported to be comparable to lipiodol-based TACE.[55] The combination of sorafenib with DEB-TACE showed promising results in a Phase II trial.[56] However, in the SPACE trial, [A Phase II Randomized, Double-blind, Placebo-controlled Study of Sorafenib or Placebo in

Table 2 Efficacy of sorafenib and TACE or SIRT in hepatocellular carcinoma (sequential therapy not included), according to current Phase I and II studies

Author	Year	Phase	Investigational drug	n	RR	DCR	OS
Britten et al[98]	2012	I	Bevacizumab + TACE	30 (15 bevacicumab)	nr	nr	49
Buijs et al[99]	2013	II	Bevacizumab + TACE	25	60	100	10.8
Pawlik et al[100]	2011	II	Sorafenib + DEB-TACE	35	58	100	nr
Cabrera et al[101]	2011	II	Sorafenib + DEB-TACE or SIRT	47	56.1	68.2	18.5
Lencioni et al[57]	2012	II	Sorafenib + DEB-TACE	307 (154 sorafenib)	nr	nr	nt
Chow et al[102]	2010	II	Sorafenib + SIRT	35	31.4	77.1	10.8
Dufour et al[54]	2010	I	Sorafenib + TACE	14	nr[a]	nr[a]	nr[a]
Erhardt et al[103]	2011	II	Sorafenib + TACE	45	2	77.8	18.5
Wu et al[104]	2012	II	Sorafenib + TACE	35	45.7	81.8	nr
Qu et al[49]	2012	II	Sorafenib + TACE	45	nr	nr	27
Park et al[46]	2012	II	Sorafenib + TACE	50	44	84	20.8
Sieghart et al[105,b]	2012	I	Sorafenib + TACE	15	46.7	53.3	10.6
Bai et al[51]	2013	II	Sorafenib + TACE	164	9.7	58.5	7.5
Chung et al[50]	2013	II	Sorafenib + TACE	147	52.4	91.2	nr
Duan et al[47]	2012	II	Sorafenib + TACE/TAE[c]	52	nr	nr	12.0

Notes: [a]The primary objective of this prospective trial was evaluation of safety and tolerability of a continuous regimen of sorafenib combined with TACE; [b]trial stopped prematurely due to safety reasons; [c]transarterial chemoperfusion in patients with pulmonary metastasis. For a better comparison of study results, efficacy according to RECIST criteria is given, as some studies used RECIST and some RECIST and modified RECIST criteria.
Adapted from Welker and Trojan.[67]
Abbreviations: DEB-TACE, drug eluting beads–transarterial chemoembolization; DCR, disease-control rate (complete response + partial response + stable disease [%]); OS, overall survival (months) – may differ between studies with respect to start point (start of therapy/diagnosis); RR, response rate (complete + partial response [%]); SIRT, selective internal radio therapy; nr, not reported; TAE, transarterial embolization; RECIST, Response Evaluation Criteria in Solid Tumors trial.

Combination With Transarterial Chemoembolization (TACE) Performed With DC Bead and Doxorubicin for Intermediate Stage Hepatocellular Carcinoma (HCC)], a randomized Phase II trial, the combination of sorafenib with DEB-TACE in intermediate-stage HCC was not meaningfully superior to DEB-TACE alone in terms of time to tumor progression and overall survival.[57] Moreover, the combination treatment was associated with an increased rate of toxicity, especially

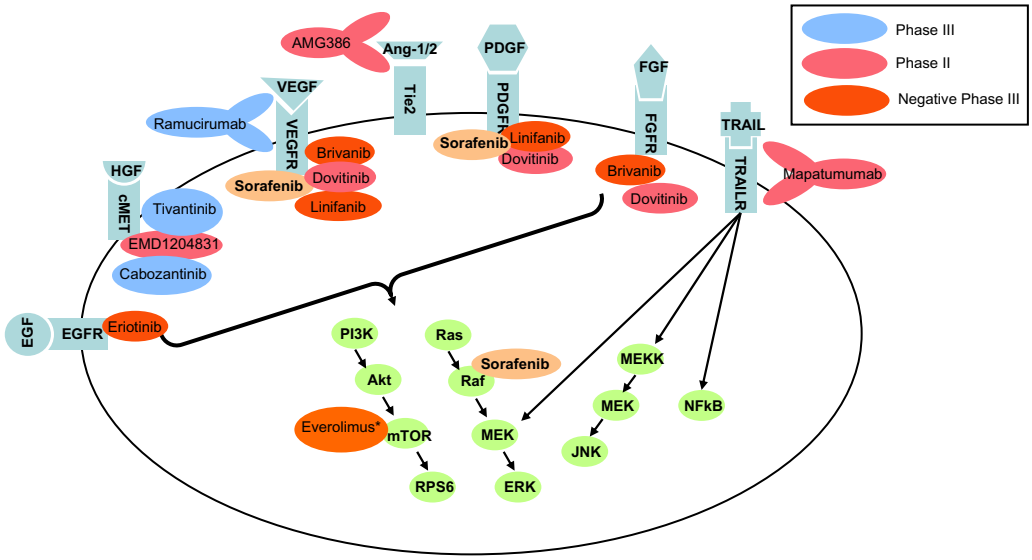

Figure 2 Molecular targets in hepatocellular carcinoma and antiangiogenic drugs according to current Phase II and Phase III studies in advanced hepatocellular carcinoma. Most agents in clinical development are antiangiogenic agents targeting angiogenesis and include different tyrosine-kinase inhibitors as well as antibodies to different cell-growth receptors. *press release (http://www.novartis.com/newsroom/media-releases/en/2013/1721562.shtml)
Abbreviations: Ang-1/2, angiopoietin-1/2; EGF(R), epidermal growth factor (receptor); ERK, extracellular-signal-regulated kinase; FGF(R), fibroblast growth factor (receptor); HGF, hepatocyte growth factor; JNK, c-Jun N-terminal kinases; mTOR, mammalian target of rapamycin; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDGF(R), platelet-derived growth factor (receptor); PI3K, phosphatidylinositide 3-kinases; RPS6, ribosomal protein S6; TRAIL, TNF-related apoptosis-inducing ligand; VEGF(R), vascular endothelial growth factor (receptor).

Table 3 Efficacy of combination therapy with systemic acting agents and targeted therapy in hepatocellular carcinoma, according to current Phase I–II studies.

Author	Year	Phase	Investigational drug	n	RR	DCR	PFS/TTP	OS
Hsu et al[106]	2010	II	Bevacizumab/capecitabine	45	9	51	2.7/nr	5.9
Sun et al[107]	2011	II	Bevacizumab/CapOx	40	20	78	6.8/nr	9.8
Thomas et al[108]	2009	II	Bevacizumab/erlotinib	40	25	67.5	9.0/nr	15.7
Kaseb et al[109]	2012	II	Bevacizumab/erlotinib	59	24	80	7.2/nr	13.7
Yau et al[110]	2012	II	Bevacizumab/erlotinib	10	0	0	1.5/1.8	4.4
Philip et al[111]	2012	II	Bevacizumab/erlotinib	27	2.1	44.4	nr/3.0	9.5
Govindarajan et al[112]	2012	II	Bevacizumab/erlotinib	21	nr	nr	nr/2.6	8.3
Treiber et al[113]	2012	II	Bevacizumab/everolimus	31	nr	nr	nr/5.8	13.3
Zhu et al[114]	2006	II	Bevacizumab/GemOx	33	18	42	5.3/nr	9.6
Berlin et al[115]	2008	II	Bortezomib/doxorubicin	39	2.3	25.6	2.4/nr	5.7
Sanoff et al[116]	2011	II	Cetuximab/CapOx	24	12.5	83	nr/4.5	4.4
Louafi et al[117,a]	2007	II	Cetuximab/GemOx	35	24	4.5	nr/nr	9.2
Asnacios et [118,a]	2008	II	Cetuximab/GemOx	45	20	40	4.7/nr	9.5
Chiorean et al[119]	2012	II	Erlotinib/docetaxel	14	0	46	3.5/nr	6.7
Luelmo et al[120]	2012	II	Everolimus/capcitabine	10	0	40	3.4/nr	nr
Knox et al[121,b]	2008	II	G3139/doxorubicin	17	0	35	nr/1.8	5.4
Yau et al[122]	2010	I/II	PTK787/doxorubicin	27	26	46	5.4/nr	7.3
Petrini et al[123]	2012	II	Sorafenib/5-fluorouracil	38	3	48	nr/7.6	12.2
Richly et al[124]	2009	I	Sorafenib/doxorubicin	18	6.3	69	4.0/nr	nr
Abou-Alfa et al[125,c]	2010	II	Sorafenib/doxorubicin	96	4	77	6.9/8.6	13.7
Dima et al[126]	2009	II	Sorafenib/mitomycin C	22	27	77	nr	nr
Prete et al[127]	2010	II	Sorafenib/octreotide	50	10	71	nr/7.0	12.0
Abou-Alfa et al[128]	2011	I	Sorafenib/PR-104	14	7	50	nr	nr
Bitzer et al[129]	2012	I/II	Sorafenib/resminostat	25	[d]	[d]	[d]	[d]
Shen et al[130,a]	2008	II	Sorafenib/tegafur-uracil	40	13	58.3	3.7/nr	nr
Hsu et [131,a]	2010	II	Sorafenib/tegafur-uracil	53	8	57	3.7/nr	7.4
Hsu et al[132]	2009	II	Thalidomide/tegafur-uracil	43	9.3	32.6	1.9/nr	4.6
Zhu et al[133]	2005	II	Thalidomide/epirubicin	19	0	41	6.0/nr	6.4

Notes: [a]Overlap of patient cohorts cannot be excluded from information provided in the abstracts; [b]trial stopped due to lack of efficacy; [c]trial stopped due to superiority of sorafenib; [d]not reported for combination subgroup. For a better comparison of study results, efficacy according to RECIST criteria is given, as some studies used RECIST and some RECIST and modified RECIST criteria. Adapted with permission from Welker MW, Trojan J. Anti-angiogenesis in hepatocellular carcinoma treatment: current evidence and future perspectives. *Word J Gastroenterol.* 2011;17:3075–3081.[67]

Abbreviations: DCR, disease-control rate (complete response + partial response + stable disease [%]); GemOx, gemcitabine and oxaliplatin; nr, not reported; OS, overall survival (months) – may differ between studies with respect to start point (start of therapy/diagnosis); PFS/TTP, progression-free survival/time to progression (months); RR, response rate (complete + partial response [%]); CapOx, capecitabine and oxaliplatin; RECIST, Response Evaluation Criteria in Solid Tumors trial; nr, not reported; HCC, hepatocellular carcinoma; nr, not reported.

in Caucasian patients.[57] In contrast, a recent cohort study showed that DEB-TACE alone was safe and associated with a median survival of 48.6 months. Therefore DEB-TACE – and also lipiodol-based TACE – seems to be an alternative treatment in patients with BCLC A-stage HCC not feasible for resection, ablation, or liver transplantation.[58] Further studies still have to establish the role of sorafenib in combination with TACE.

Strategies to overcome resistance to antiangiogenic treatment

Since tumor angiogenesis is a complex process based not only on VEGF, but on a subtle interplay of intricately interweaved pathways, targeting different drivers of tumor angiogenesis might overcome antiangiogenic resistance. VEGFR2 is the critical receptor involved in tumor angiogenesis, with its activation inducing a number of other cellular modifications, resulting in tumor growth and metastases. Ramucirumab (IMC-1121B) is a fully human monoclonal antibody developed to specifically inhibit VEGFR2. Ramucirumab is currently being investigated in multiple clinical trials across a variety of tumor types, including a placebo-controlled Phase III trial in patients with HCC after failure of sorafenib. Results of this trial are expected early next year (http://clinicaltrials.gov/show/NCT01140347).

Another important regulator of vessel remodeling and maturation is the angiopoietin/Tie ligand/receptor system, which is an attractive therapeutic target in cancer.[59] In theory, angiopoietin inhibitors could inhibit tumor angiogenesis efficiently, but may lack typical tyrosine-kinase receptor inhibitor-associated toxicity. Currently, the selective angiopoietin 1/2-neutralizing peptibody AMG 386 is being investigated

in combination with sorafenib in a Phase II trial in advanced or inoperable HCC (http://www.clinicaltrials.gov/ct2/show/NCT00872014). Completion of this study is also expected in the near future.

The most promising target in HCC is currently MET, a proto-oncogene that encodes a protein known as hepatocyte growth-factor receptor.[60,61] Activation of MET signaling leads to tumor-cell growth, tumor-cell migration and invasion, and angiogenesis.[62] In HCC, aberrant MET signaling is frequently found, and MET overexpression is associated with advanced tumor stage and poor prognosis.[63–65] Tivantinib (ARQ 197) is an oral, selective MET tyrosine-kinase inhibitor that is developed in non-small-cell lung cancer, colorectal cancer, and HCC.[62,66] Recent data from a randomized placebo-controlled Phase II study in advanced HCC after sorafenib failure demonstrated a benefit of patients with MET-high HCC only.[65] In this study, the median time to progression was 2.7 months in the tivantinib arm and 1.4 months in the placebo arm, and median overall survival was 7.2 months and 3.8 months, respectively, in the small group of patients with MET-high tumors. Of note, severe neutropenia developed in a substantial proportion of patients, and the dose of tivantinib was reduced from 360 mg to 240 mg for the further development of tivantinib in HCC. Recently, a randomized Phase III trial with tivantinib vs placebo in advanced MET-high HCC after failure of sorafenib was started (http://clinicaltrials.gov/show/NCT01755767). Cabozantinib, an oral inhibitor of RET ("rearranged during transfection"), VEGFR2, and MET is currently also being developed in a randomized Phase III trial in advanced HCC after sorafenib failure.

Further promising drugs that are under development for advanced HCC are the multiple tyrosine-kinase inhibitor dovitinib,[134] the oral histone-deacetylase inhibitor resminostat (http://clinicaltrials.gov/show/NCT00943449), and RO5137382 (GC33), a humanized anti-glypican-3 monoclonal antibody (http://www.clinicaltrials.gov/ct2/show/study/NCT01507168). An overview of current molecular targets and targeted drugs in HCC is given in Figure 2. Another approach to overcome resistance to antiangiogenic therapy is combination of targeted therapy with other systemic agents (Table 3). Currently, the efficacy and safety of these combination therapies cannot comprehensively rated, since only data from Phase I and II studies have been reported.

Summary

The multikinase inhibitor sorafenib is still the only approved drug for advanced HCC. Data concerning the combination of sorafenib with locoregional therapies are still controversial. Multiple clinical trials are currently investigating new antiangiogenic drugs, especially in patients after failure of sorafenib. Inhibition of VEGFR2, MET, or angiopoietin, either alone or in combination with sorafenib, are promising approaches that might ultimately improve the prognosis of advanced HCC.

Disclosure

MW Welker received honoraria from Bayer Health Care. J Trojan received honoraria from Bayer Health Care and served on the advisory boards for Bayer Health Care, Daiichi Sankyo, Lilly Imclone, Novartis, Bristol-Myers Squib, and Roche. The authors report no other conflicts of interest in this work.

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