Review

Clinical Cancer Research

The Role of Angiogenesis in Hepatocellular Carcinoma

Michael A. Morse[1], Weijing Sun[2], Richard Kim[3], Aiwu Ruth He[4], Paolo B. Abada[5], Michelle Mynderse[6], and Richard S. Finn[7]

Abstract

Hepatocellular carcinoma (HCC) accounts for about 90% of all primary liver cancers and is the second leading cause of cancer-related deaths worldwide. The hypervascular nature of most HCC tumors underlines the importance of angiogenesis in the pathobiology of these tumors. Several angiogenic pathways have been identified as being dysregulated in HCC, suggesting they may be involved in the development and pathogenesis of HCC. These data provide practical targets for systemic treatments such as those targeting the vascular endothelial growth factor receptor and its ligand. However, the clinical relevance of other more recently identified angiogenic pathways in HCC pathogenesis or treatment remains unclear. Research into molecular profiles and validation of prognostic or predictive biomarkers will be required to identify the patient subsets most likely to experience meaningful benefit from this important class of agents.

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer mortality (1). Most patients with HCC present with advanced disease (2), and the 5-year overall survival (OS) rates are 10% for locally advanced and 3% for metastatic disease (3). Although HCC follows diverse causes of liver damage (including chronic alcohol use, chronic hepatitis B and C infection, and nonalcoholic fatty liver disease; ref. 4), common associated findings are hypervascularity and marked vascular abnormalities (5), such as arterialization and sinusoidal capillarization (6). Increased tumor vascularity may result from sprouting angiogenesis or by recruiting existing vessels into the expanding tumor mass (a process called co-option). This review addresses the molecular underpinnings of angiogenesis in advanced HCC, current approaches to targeting angiogenesis (Table 1), novel strategies in development, and prospects for combining antiangiogenic therapy with other systemic modalities.

Angiogenesis and Angiogenic Targets in Advanced HCC

Hypoxia is presumed to robustly stimulate tumor angiogenesis (17, 18). Several animal models examining the hypoxic tumor microenvironment in HCC with small fiberoptic sensors or radiographic imaging with oxygen-sensitive probes have shown intratumor oxygen values that were significantly lower than those in normal liver tissue (18–20). Direct evidence of hypoxia in human HCC is sparse, and results have not been as clear (21). Most HCC *in vitro* and *in vivo* models investigating hypoxia-mediated mechanisms in HCC focus on the upregulation of hypoxia-inducible factor proteins, which induce expression of proangiogenic factors, including vascular endothelial growth factor (VEGF), that promote angiogenesis in HCC tumors (17, 18, 22, 23). At the molecular level, angiogenesis results from an imbalance between drivers of vessel growth and maturation [VEGF-A, -B, -C, and -D, fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), angiopoietins, hepatocyte growth factor, endoglin (CD105), and others] and inhibitors (angiostatin, endostatin, thrombospondin-1, and others). Proangiogenic factors activate endothelial cell tyrosine kinases and subsequent downstream intracellular signaling through mitogen-activated protein kinase and phosphatidylinositol-3-kinases (PI3K)/Akt/mTOR pathways leading to angiogenesis (24). The complexity and potential synergism of these pathways that stimulate angiogenesis have prompted the development of multiple antiangiogenic therapies over the last several decades.

In fact, most currently approved treatments for advanced HCC in the first- and second-line settings target angiogenic pathways. Of the known or potential angiogenic pathways in tumors, the VEGF/VEGF receptor (VEGFR) signaling pathway has been validated as a drug target in HCC (7, 14). The first breakthrough systemic therapy for treating advanced HCC was sorafenib (4), a multikinase inhibitor that disrupts VEGFR signaling as well as several other targets involved in angiogenesis (ref. 7; Table 1). Other molecular pathways that may have angiogenic effects are specifically targeted by several agents under investigation

[1]Department of Medicine, Division of Medical Oncology, Duke University Health System, Durham, North Carolina. [2]Division of Medical Oncology, University of Kansas School of Medicine, Kansas City, Kansas. [3]Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida. [4]Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia. [5]Eli Lilly and Company, Indianapolis, Indiana. [6]Syneos Health, Clinical Solutions, Raleigh, North Carolina. [7]Department of Medicine, Division of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, California.

Note: Current address for M. Mynderse: PRA Health Sciences, Raleigh, North Carolina.

Corresponding Author: Michael A. Morse, Department of Medicine, Division of Medical Oncology, Duke University Health System, Duke Box 3233, Durham, NC 27710. Phone: 919-681-3480; E-mail: michael.morse@duke.edu

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Table 1. Antiangiogenic therapies evaluated in phase III trials for treatment of HCC

Compound	Type	Target(s)	Phase	Treatment line	Regimen	*N*	mOS (mos)	HR (95% CI), *P*	mPFS (mos)	HR (95% CI), *P*	ORR (%)	DCR (%)
Sorafenib (7)	TKI	VEGFR-1–3, PDGFR-β, c-Kit, FLT-3, RET, Raf-1, B-Raf	III	1st line	Sorafenib	299	10.7	0.69 (0.55–0.87), <0.001	5.5	0.58 (0.45–0.74), <0.001	2	43[a]
					Placebo	303	7.9		2.8		1	32[a]
Regorafenib (8)	TKI	VEGFR-1–3, PDGFR-β, FGFR1, CD117, RET, B-Raf, TIE2	III	2nd line	Regorafenib	379	10.6	0.63 (0.50–0.79), <0.0001	3.1	0.46 (0.37–0.56), <0.0001	11[b]	65[b,c]
					Placebo	194	7.8		1.5		4[b]	36[b,c]
Sunitinib (9)	TKI	VEGFR-1–3, PDGFR, c-Kit, FLT-3, RET	III	1st line	Sunitinib	530	7.9	1.30 (1.13–1.50), 0.0014	3.6	1.13 (0.99–1.30), 0.229	6.6	50.8[d]
					Sorafenib	544	10.2		3.0		6.1	51.5[d]
Brivanib (10)	TKI	VEGFR, FGFR	III	1st line	Brivanib	577	9.5	1.07 (0.94–1.23), 0.312	4.2[e]	1.01 (0.88–1.16), 0.853	9[b]	65[b]
					Sorafenib	578	9.9		4.1[e]		12[b]	66[b]
Brivanib (11)	TKI	VEGFR, FGFR	III	2nd line	Brivanib	263	9.4	0.89 (0.69–1.15), 0.331	4.2[e]	0.56 (0.42, 0.76), <0.001	10	61
					Placebo	132	8.2		2.7[e]		2	40
Linifanib (12)	TKI	VEGFR, PDGFR	III	1st line	Linifanib	514	9.1	1.05 (0.90–1.22), ns	5.4	0.76 (0.64–0.90), 0.001	13.0	NR
					Sorafenib	521	9.8		4.0		6.9	NR
Lenvatinib (13)	TKI	VEGFR-1–3, FGFR-1–4, PDGFR-α, RET, c-Kit	III	1st line	Lenvatinib	478	13.6	0.92 (0.79–1.06)	7.4	0.66 (0.57–0.77), <0.001	24.1[b,f]	75.5[b,f]
					Sorafenib	476	12.3		3.7		9.2[b,f]	60.5[b,f]
Ramucirumab (14)	IgG_1 mAb	VEGFR-2	III	2nd line	Ramucirumab	283	9.2	0.87 (0.72–1.05), 0.14	2.8	0.63 (0.52–0.75), <0.0001	7.1	56.2
					Placebo	282	7.6		2.1		0.7	45.7
Ramucirumab (15)	IgG_1 mAb	VEGFR-2	III	2nd line; only patients with baseline AFP >400 ng/mL	Ramucirumab	197	8.5	0.71 (0.53–0.95), 0.0199	2.8	0.45 (0.34–0.60), <0.0001	4.6	60
					Placebo	95	7.3		1.6		1.1	39
Cabozantinib (16)	TKI	c-Met, VEGFR-2, c-Kit, RET, FLT-3, TIE2, Axl	III	2nd line or 3rd line	Cabozantinib	470	10.2	0.76 (0.63–0.92), 0.0049	5.2	0.44 (0.36–0.52), 0.001	4	64
					Placebo	237	8.0		1.9		0.4	33

Abbreviations: AFP, α-fetoprotein; CI, confidence interval; DCR, disease control rate; FGFR(1–4), fibroblast growth factor receptor; HR, hazard ratio; mAb, monoclonal antibody; mOS, median overall survival; mos, months; mPFS, median progression-free survival; *N*, number of subjects; ns, not significant; NR, not reported; ORR, objective response rate; PDGFR(-α, -β), platelet-derived growth factor receptors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR(1–3), vascular endothelial growth factor receptor.

[a]Disease-control rate was the percentage of patients who had a best-response rating of complete or partial response or stable disease that was maintained for at least 28 days after the first demonstration of that rating on independent radiologic review.

[b]Response based on modified RECIST criteria.

[c]Defined as patients with complete response, partial response, or stable disease maintained for ≥6 weeks.

[d]Defined as patients with complete response, partial response, or stable disease maintained for ≥12 weeks.

[e]Time to progression.

[f]Posthoc analysis of response using RECIST v1.1 ORR: 18.8% versus 6.5%; DCR: 72.8% versus 59.0%.

(Table 1). Despite an initial breakthrough for the field, survival benefits observed with tyrosine kinase inhibitors (TKI) such as sorafenib have been modest. Strategies for overcoming the high rate of acquired resistance to sorafenib, targeting other elements of angiogenic pathways alone or with other novel therapies, and the investigation of biomarkers that may predict the efficacy of these therapies are under development. In this section, we briefly review proven and potentially clinically relevant angiogenic pathways for HCC. Details about each drug, drug targets, and clinical trial outcomes are included in Table 1.

VEGF/VEGFR

Both VEGF and VEGFRs, the most prominent and well-researched regulators of angiogenesis (2), are critical for HCC growth and development. The ligands VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E and placental-growth factors-1 and -2 are members of a family of structurally related dimeric proteins (25). VEGFR-2, which is expressed on nearly all endothelial cells, is stimulated by binding to either VEGF-A, VEGF-C, or VEGF-D (25), with VEGF-A being the most critical ligand. This binding leads to a phosphorylation cascade that triggers downstream cellular pathways, ultimately resulting in endothelial proliferation and migration, and formation and branching of new tumor blood vessels necessary for rapid tumor growth and dissemination (25).

These vessels have abnormally leaky vasculature, partially due to the overexpression of VEGF (5), resulting in areas of high interstitial pressure and severe hypoxia or necrosis, both of which can further drive malignant potential (5).

Circulating VEGF levels are increased in HCC and have been shown to correlate with tumor angiogenesis and progression (26, 27). Observations of an association between high tumor microvessel density and increased local and circulating VEGF with rapid disease progression and reduced survival (26, 27) supported the evaluation of VEGF-pathway–directed therapies for HCC. Preclinical studies also support targeting the VEGF axis in HCC (28).

PDGF/PDGFR

The PDGF family consists of PDGF-A, PDGF-B, PDGF-C, and PDGF-D polypeptide homodimers and the PDGF-AB heterodimer (29). Binding of PDGFs to the PDGF receptor (PDGFR)-α and -β tyrosine kinase receptors expressed on other mesenchymal cells, such as fibroblasts, smooth muscle cells, and pericytes, activates pathways that are the same as or similar to those stimulated by VEGF (29, 30). In human HCC, overexpression of PDGFR-α is correlated with microvessel density and worse prognosis. A potential interaction of PDGFR and VEGFR signaling is suggested by the observation that PDGFR-α, PDGFR-β, and VEGF coexpression was associated with poor survival of HCC patients. However, the clinical relevance of the PDGF pathway as a target for inhibition of angiogenesis in HCC remains unclear. Although sorafenib and other TKIs may include PDGFR as a target, TKIs also inhibit other pathways; so, the relative impact from inhibition of the PDGF pathway to the overall clinical benefit is unknown.

FGF/FGFR

FGFs are heparin-binding growth factors that comprise a family of 22 members and function as ligands for 4 receptor tyrosine kinases, FGFR-1, -2, -3, and -4 (31). Both FGFs and FGFRs are ubiquitously expressed and have numerous functions, including regulation of cell growth and differentiation of angiogenesis (32).

Cross-talk between FGF-2 and VEGF-A during initial phases of tumor growth induces neovascularization and further tumor growth (33). FGF-2 and VEGF-A are associated with increased capillarized sinusoids in HCC tumor angiogenesis (34), and FGF stimulation modulates integrin expression that regulates endothelial cells in the microenvironment, thus altering cellular parameters necessary for angiogenesis. The potential synergism between the FGF and VEGF pathways may contribute to the resistance of advanced HCC tumors to the VEGF inhibitor sorafenib (35, 36). However, the role of FGF-1 and -2 in angiogenesis remains unclear (37). In contrast, other FGF/FGFR combinations may be more relevant for their effect on HCC proliferation. For example, FGF-19 activates FGFR-4 (38) and FGF-19 amplification was associated with a positive response to FGF-19–targeted small molecules (39, 40).

Angiopoetin/Tie pathway

Angiopoietin 1 (Ang1) and 2 (Ang2) are ligands for the Tie2 receptor on endothelial cells that promote angiogenesis (41). Although Ang1 is widely expressed in vascular support cells, Ang2 expression is limited to sites of vascular remodeling (42). Ang2 and Ang1 have similar binding affinity for Tie2. Ang2 antagonizes Ang1-mediated activation of Tie2, and this interaction likely modulates the pathway. In normal tissue, Ang1 appears to work to stabilize blood vessels, and increased Ang2 expression in areas of remodeling inhibits this interaction, destabilizing blood vessel support cells, a step necessary to facilitate vessel proliferation or sprouting in the presence of VEGF (42).

Ang2 levels were observed to be increased in cirrhosis, and even more so in HCC, suggesting the angiopoietin pathway may play a role in tumor angiogenesis, potentially in coordination with VEGF ligands (41). Although some agents targeting this pathway alone or combined with sorafenib have been tested in the clinic (43), any potential clinical benefit remains to be proven.

Endoglin (CD105)

Endoglin (CD105), upregulated in proliferating endothelial cells, including that of HCC (44, 45), is an accessory coreceptor for transforming growth factor-β. Endoglin not only antagonizes the inhibitory effects of transforming growth factor-β (TGFbeta; ref. 46), it controls the endothelial progenitor transition to functional epithelial cells (47).

Expression of endoglin correlated with stage, tumor differentiation, and aggressive tumor behavior of HCC. CD105 promotes the invasion and metastasis of liver cancer cells by increasing VEGF expression (48). Despite these observations, the clinical relevance of targeting this pathway is still unclear (49).

Angiogenic Biomarkers for HCC

Identifying tumors most sensitive to antiangiogenic therapy could improve therapeutic approaches. The search for potential predictive markers has emphasized the target or target receptors, with the VEGF pathway components being the primary focus (25); yet this search has yielded little success (50–53).

VEGF-A has been assessed as a potential prognostic and predictive biomarker for benefit from the VEGF-targeted monoclonal antibody bevacizumab across multiple tumor types. However, reassessing VEGF-A as a predictive biomarker for bevacizumab showed that the VEGF-A level was not a robust predictive biomarker for bevacizumab activity, and that patient stratification

based on a single baseline VEGF-A measurement is unlikely to be implemented successfully in clinical practice (54). In HCC specifically, exploratory analyses of the SHARP trial identified plasma concentrations of VEGF and Ang2 as independently prognostic for survival in patients with advanced HCC, although neither predicted treatment response or benefit (55). Recently, Horwitz and colleagues hypothesized that amplification of VEGF-A in human HCC may predict OS in patients treated with sorafenib (56). In their study, they observed increased tumor sensitivity with VEGF-A amplification to VEGFR-inhibiting agents such as sorafenib (56). Inhibition of VEGFR on endothelial cells by sorafenib was hypothesized to suppress hepatocyte growth factor secretion and any subsequent proliferative effects on tumor cells (56). Although initially promising, evaluation of this genetic alteration in the adjuvant STORM study was not associated with benefit (57).

Elevated serum α-fetoprotein has long been associated with poor prognosis in HCC (4) and has been correlated with elevated VEGFR expression and increased angiogenesis (58). Profiling studies also suggest that tumors expressing α-fetoprotein may be a biologically different subtype of HCC (59). In the phase III HCC study, REACH, a subgroup analysis suggested that an OS benefit was primarily in the subpopulation of patients who had elevated baseline α-fetoprotein concentrations (14). A recent phase III trial (REACH-2; NCT02435433) evaluated α-fetoprotein as a candidate biomarker of patient selection for ramucirumab treatment (15). For patients with advanced HCC previously treated with sorafenib and with baseline α-fetoprotein $\geq$400 ng/mL, treatment with ramucirumab demonstrated significantly longer OS and progression-free survival than those treated with placebo, confirming this strategy for patient selection (15). One hypothesis to explain this observation is that inhibition of VEGFR-2 signaling is more effective in this subtype (14). These data suggest that this may be an alternative strategy to identify the subset of patients most likely to benefit from a selective VEGFR-2 targeting agent. Although this effect has not been observed with other small-molecule inhibitors of VEGFR-2, all other VEGFR-2 agents with proven activity in HCC inhibit additional pathways that may further modulate their activity in different subgroups.

In addition to baseline levels of α-fetoprotein, other factors including the cause of liver disease, presence of hypertension or hand–foot syndrome, and a variety of other blood- or tissue-based biomarkers may have a potential predictive association with antiangiogenic treatment efficacy (60–67). For example, a recent exploratory analysis of the RESORCE trial has suggested that decreased expression of lectin-like oxidized LDL receptor 1 (LOX-1), Ang1, cystatin-B, latency-associated peptide TGFβ1, or macrophage inflammatory protein 1α may be predictive of the OS and TTP treatment benefit observed from regorafenib (68). However, apart from α-fetoprotein and ramucirumab, no other biomarker or characteristic has been prospectively validated as a method to select patients appropriate for a systemic therapy.

Antiangiogenic Therapies in HCC

Although several antiangiogenic agents have been tested in HCC or are under development, sorafenib and regorafenib are the only currently globally approved antiangiogenic agents shown to improve survival in patients with advanced HCC.

Sorafenib

Sorafenib is an oral multikinase inhibitor that targets VEGFR-1, VEGFR-2, and VEGFR-3; PDGFR-β; c-Kit; FLT-3; RET; and Raf-1 (69). The phase III SHARP study (7) enrolled patients with advanced HCC not previously treated with systemic therapy, Eastern Cooperative Oncology Group performance status of 2 or less, and liver function of Child–Pugh class A (Table 1). In SHARP, sorafenib demonstrated a modest survival benefit of 2.8 months over placebo for patients with advanced HCC. Treatment-related adverse events were more frequent in the sorafenib group (80% vs. 52%) and included diarrhea, weight loss, hand–foot skin reaction, and hypophosphatemia. Dose reductions and interruptions were common in the sorafenib arm, with higher rates of discontinuation of the study drug due to adverse events related to study treatment in the sorafenib arm (11% vs. 5%; ref. 7). Similar results were observed in a second phase III trial that enrolled only patients from the Asia-Pacific region (69). Sorafenib benefited patients with HCC regardless of etiology, although patients with hepatitis C seem to have received a greater benefit (65).

Regorafenib

Regorafenib is a multikinase inhibitor that targets VEGFR, c-Kit, RET, B-Raf, PDGFR, and FGFR1. Regorafenib was recently approved to treat patients with advanced HCC who progressed on sorafenib based on results from both a phase II study and a phase III trial (RESORCE; ref. 8; Table 1). Regorafenib was the first treatment demonstrating a survival benefit for patients with advanced HCC after progression on sorafenib. In the regorafenib arm, hypertension, hand–foot skin reaction, fatigue, and diarrhea were more common (8). Additional analyses showed a median OS over 24 months across both lines of therapy with first-line sorafenib and second-line regorafenib (70). Of note, eligible patients for RESORCE were required to be tolerant of sorafenib for a minimal period of time, and patients intolerant to sorafenib were excluded (8).

Sunitinib

Sunitinib, an oral inhibitor of PDGFR; VEGFR-1, -2, and -3; c-Kit; fms-like tyrosine kinase-3 (FLT-3); and the glial cell line–derived neurotrophic factor receptor (RET; ref. 9), failed in a phase III head-to-head comparison with sorafenib (Table 1). Median OS was unexpectedly longer with sorafenib than sunitinib in patients with locally advanced or metastatic HCC (9). In both phase II trials assessing sunitinib in advanced HCC, a 6% to 11% mortality rate linked to liver toxicity was observed, and, in retrospect, may have been a missed warning (66, 71).

Brivanib

Brivanib, a selective VEGFR and FGFR inhibitor and multikinase inhibitor, did not improve OS compared with placebo as adjuvant therapy for patients with unresectable intermediate stage HCC after TACE (72). It also failed to demonstrate noninferiority for OS in a phase III comparison with first-line sorafenib in patients with advanced HCC (ref. 10; Table 1). A phase III trial in the second-line setting against placebo also did not meet its endpoint of OS prolongation for patients with advanced HCC who were intolerant to or progressed on/after sorafenib (ref. 11; Table 1). The failure of the second-line phase III trial is attributed to enrichment of indolent HCC (positive selection bias) and potential imbalance in prognostic factors such as portal vein invasion (73). The most common treatment-emergent

adverse events included hypertension, fatigue, hyponatremia, decreased appetite, asthenia, diarrhea, increased aspartate aminotransferase, and increased alanine aminotransferase (11).

Linifanib

Linifanib is a novel adenosine triphosphate-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases, but has no significant effect on cytosolic tyrosine or serine-threonine kinases (12). A phase III study in treatment-naïve patients with unresectable or metastatic HCC comparing linifanib with sorafenib did not meet its primary endpoint of noninferiority in OS (ref. 12; Table 1). The trial was halted because of futility, and drug toxicity was also a concern. The most common treatment-emergent adverse events included hypertension, palmar-plantar erythrodysesthesia syndrome, increased aspartate aminotransferase, and diarrhea (12).

Ramucirumab

Ramucirumab, an IgG1 monoclonal antibody and VEGFR-2 antagonist, improved OS in a phase III study of patients who had progressed on or were intolerant to sorafenib with baseline α-fetoprotein ≥400 ng/mL (REACH-2; ref. 15). Hypertension and hyponatremia were the only adverse events grade ≥3 in ≥5% of patients in the ramucirumab arm. The approach to select patients based on baseline α-fetoprotein was based on the prior phase III study REACH (14). Although the REACH trial did not demonstrate a statistically significant improvement in OS in the ITT population, a survival benefit was observed in the subgroup of patients with a higher baseline α-fetoprotein (≥400 ng/mL) treated with ramucirumab (refs. 14, 15; Table 1). No OS benefit was observed in patients with α-fetoprotein <400 ng/mL (14). REACH-2 confirmed the survival benefit in patients with baseline α-fetoprotein ≥400 ng/mL first observed in REACH, and is the first positive trial in a biomarker-selected population with this disease (14, 15).

Cabozantinib

Cabozantinib is a TKI with the unique characteristic of inhibiting c-Met in addition to VEGFR-2, c-Kit, RET, FLT-3, Tie2, and Axl. Potential activity was observed in a phase II trial (74). A subsequent phase III CELESTIAL trial compared cabozantinib with placebo as treatment of advanced HCC after progression on up to two previous lines of treatment, one of which must have included sorafenib (ref. 16; Table 1). The trial met the primary endpoint of improved OS (16). In the cabozantinib arm, hand–foot skin reaction, hypertension, increased aspartate aminotransferase, fatigue, and diarrhea were common (16).

Lenvatinib

Lenvatinib is a multikinase inhibitor with multiple targets, including VEGFR-1, -2 and -3; FGFR-1, -2, -3, and -4; PDGFR-α; RET; and c-Kit. Positive results were seen in a phase II study for patients with advanced HCC in Japan and South Korea (75). Recently, a phase III study of lenvatinib versus sorafenib for patients with unresectable HCC demonstrated that lenvatinib is noninferior in OS to sorafenib (ref. 13; Table 1). The most common treatment-emergent adverse events in the lenvatinib arm were hypertension, diarrhea, decreased appetite, decreased weight, and fatigue (13).

Of note, the trial did not allow tumors with ≥50% liver occupation or portal vein invasion at the main portal branch (NCT01761266), and so some patients with poorer prognosis were excluded. Despite this issue, lenvatinib is the only agent in a positive first-line trial to be tested against a proven active control arm, sorafenib.

Several other antiangiogenic treatments have been tested in patients with advanced HCC and either did not meet the primary endpoints or failed to show noninferiority to sorafenib despite promising results in early-phase trials.

Future Directions

The role of antiangiogenic therapy in treating HCC is well established and accepted (76). However, initial resistance or development of resistance remains a major problem, and substantial improvements beyond what has been observed with current antiangiogenic agents have been difficult to achieve. Angiogenesis is a complex process with multiple different pathways potentially involved. New agents or combinations of synergizing agents with differing or broader selectivity to inhibit a variety of angiogenic pathways, or targeting agents to specific populations with a sensitizing mutation may potentially overcome initial or acquired resistance to initial antiangiogenic inhibitor treatment. Some agents are already demonstrating encouraging results in the laboratory and clinic (13, 36, 43, 77–79).

Patients with advanced HCC and preserved hepatic function should be considered for treatment with systemic therapy. As more treatment options for HCC become available, a strategy for long-term management and a sequential treatment algorithm need to be developed. Systemic therapy with sorafenib has become the standard first-line treatment for patients with advanced disease (7). More recently, lenvatinib was shown to be noninferior to sorafenib as first-line therapy (13) and, if globally approved, will be an additional first-line treatment option. Currently, regorafenib is a globally approved treatment option for patients who progress on sorafenib (8); nivolumab is another option approved in the United States. If approved, cabozantinib could be an additional second-line choice after sorafenib, and ramucirumab is an option after sorafenib in patients with elevated α-fetoprotein (15, 16). No head-to-head data comparing regorafenib, nivolumab, cabozantinib, or ramucirumab exist. In the absence of data, other information including the respective toxicity profiles, biomarker data, and characteristics of the respective study populations will be important considerations when making clinical treatment decisions and deciding the future sequential use of the various agents. Such a strategy is already being applied in treatment algorithms for patients with renal cell carcinoma (80) as well as other solid tumors.

Determination of the best sequential or combination strategies of antiangiogenic agents with newer immuno-oncology agents or other agents with novel mechanisms of action will be an important avenue of exploration. The anti-programmed death receptor (PD)-1 antibody nivolumab was recently approved by the FDA for patients with HCC who have been previously treated with sorafenib (81). Trials with pembrolizumab (82), an anti–PD-1 antibody, and durvalumab (83), an anti–PD-L1 antibody, alone or with the anti-CTLA4 monoclonal antibody tremelimumab (84), have produced similar response rates in patients with advanced HCC. To leverage potential synergistic effects of antiangiogenic therapy with immunotherapy, ongoing trials are assessing combinations of lenvatinib with pembrolizumab (NCT03006926), regorafenib with pembrolizumab (NCT03347292), atezolizumab with bevacizumab

(NCT02715531 and IMbrave150; NCT03434379), and ramucirumab with durvalumab (NCT02572687). Preliminary results from the phase Ib study of patients with unresectable HCC treated with lenvatinib plus pembrolizumab demonstrated this combination was well tolerated by these patients and had encouraging antitumor activity with a response rate of 46% (85). Similarly, a phase Ib study of bevacizumab plus atezolizumab demonstrated acceptable toxicity and a 62% response rate for patients with previously untreated unresectable or metastatic HCC (86). This study informed the decision to evaluate bevacizumab plus atezolizumab compared with sorafenib alone in a phase III study of patients with systemic treatment-naïve, locally advanced, metastatic, and/or unresectable HCC (IMbrave150; NCT03434379; ref. 87).

Other potential immunotherapeutic strategies in HCC include cancer vaccines targeting antigens expressed by HCC, adoptive transfer of T cells and cytokine-induced killer cells, oncolytic viruses, and other immune modulators (88). Immunotherapeutic therapies rely on trafficking T cells to the tumor and on facilitating an immunostimulatory environment; antiangiogenics may facilitate T-cell trafficking and further enhance immunotherapy-based approaches (89).

VEGF signaling has multiple effects on immune cells, including inhibition (90) of dendritic cells. VEGF signaling can induce dendritic cells to produce the tolerogenic enzyme indoleamine 2,3-dioxygenase (91), impair T-cell infiltration into tumors (92), and cause upregulation of immune checkpoints on $CD8^+$ T cells (93), resulting in the modulation of T-cell differentiation and cytotoxic T-cell function (94). Therefore, inhibition of VEGF signaling may abrogate some of these immunosuppressive effects, further enhancing immunotherapeutic treatments, and is a topic of much preclinical and translation research.

However, whereas anti-VEGF therapy may improve immune responses, excessive inhibition of angiogenesis may increase hypoxia in the tumor microenvironment and subsequently increase immunosuppression (95–97). Additionally, the VEGFR TKIs also target other tyrosine kinases that could have other, and at times contradictory, effects on the immune response (98, 99). Further studies are needed to establish the optimal dose, schedule, class of drug, and safety of combining immunotherapy with anti-VEGF therapy in HCC and other cancer types.

The ongoing search for predictive and prognostic biomarkers for advanced HCC will allow clinicians and researchers to enrich future clinical trials based on molecular data; however, current biomarker data do not sufficiently inform these decisions. Due to the molecular heterogeneity of advanced HCC, genome-wide studies may be key to identifying molecular signatures of genes that are recurrently altered in advanced tumors, to providing actionable information about predictive or prognostic markers, and to increasing our knowledge of potential new drug targets (100–102). In fact, sequencing of more than 200 surgically resected liver tumors identified several risk factor–specific gene signatures and mutations characteristic of the HCC stage that may help inform future biomarker analyses (103). Targetable alterations, in particular amplifications in *VEGF-A* and the *FGF-CCND1* locus that contains *FGF3*, *FGF4*, and *FGF19*, were associated with advanced-stage tumors. Small noncoding RNAs, or microRNAs (miRNA), regulate gene expression at the translational or posttranslational levels and are associated with the molecular mechanisms of HCC development (103). Aberrant expression of multiple miRNAs effect processes such as angiogenesis (104–107). The high stability of miRNAs in circulation would make them useful biomarkers; more research is needed to validate these studies. The molecular heterogeneity of advanced HCC combined with multiple complex pathways involved with angiogenesis will continue to challenge the identification of useful and reliable biomarkers that will benefit patients. In fact, several circulating miRNAs may predict OS for patients treated with regorafenib (67). The search for novel targets and predictors of prognosis through molecular profiling is an important goal. The identification of circulating tumor products in the blood, such as RNA-based signatures or circulating tumor DNA, is still a subject of research in liver cancer (108, 109).

Although inhibition of angiogenesis to treat HCC has been successfully translated into clinical use, a better understanding of the molecular underpinnings of angiogenesis in HCC should allow further progress in utilizing this class of treatments. Current approaches to targeting angiogenesis, including novel strategies in development, the search for predictive biomarkers, and the prospects for combining antiangiogenic therapy with other systemic modalities such as immunotherapy, should contribute to improving the outcome of patients with HCC.

Disclosure of Potential Conflicts of Interest

M.A. Morse is a consultant/advisory board member for Eli Lilly. W. Sun is a consultant/advisory board member for Bayer. R. Kim reports receiving speakers bureau honoraria from Eli Lilly and is a consultant/advisory board member for Bayer, Bristol-Myers Squibb, Eli Lilly, and Taiho. P.B. Abada is senior medical director at Eli Lilly and holds ownership interest (including patents) in Eli Lilly. R.S. Finn is a consultant/advisory board member for AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Eli Lilly, Merck, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

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