The Role of Tyrosine Kinase Inhibitors in Hepatocellular Carcinoma

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Abstract: Since the approval of the multityrosine kinase inhibitor (TKI) sorafenib (Nexavar, Bayer and Onyx) as the standard of care for intermediate to advanced stages of hepatocellular carcinoma (HCC), there has been considerable interest in developing more potent TKIs to improve morbidity and mortality for patients with HCC. Much of the research on TKIs targets pathways implicated in angiogenesis, given that HCC is a highly vascularized cancer type. It was theorized that the efficacy of sorafenib is primarily attributable to its angiogenesis targets—namely, vascular endothelial growth factor receptors, platelet-derived growth factor receptors, FLT-3, and RAF kinases. Over the past 2 years, several pivotal phase 3 trials of newer TKIs targeting similar pathways have failed to meet criteria for superiority or noninferiority to sorafenib. Reasons for this may stem from the genetic and biologic heterogeneity of HCC. Genomic studies of tumor samples have shown scarce uniformity in kinase mutations, underscoring the variability that exists in HCC. This beckons the question of whether efforts should shift to other potential targets, either within the realm of TKIs or other targets entirely. Receptor tyrosine kinases, such as those encoded by the MET proto-oncogene, are expressed in certain individuals and have shown to be susceptible to targeted TKIs. As researchers continue to investigate therapies, the goal is to further research efforts into culprit oncogenes that mediate tumor progression, which will likely lead to more personalized and targeted regimens.

Keywords
Neoadjuvant therapy, renal cell carcinoma, presurgical therapy, kidney cancer

Introduction

Sorafenib (Nexavar, Bayer and Onyx)—a tyrosine kinase inhibitor (TKI) of BRAF, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR)—is currently the standard of care in unresectable hepatocellular carcinoma (HCC), after it was found to significantly increase median overall survival of patients with advanced HCC from 7.9 months to 10.7 months.[1] Its success has driven continuing interest in developing more potent and targeted TKIs and investigating the efficacy of combination regimens with TKIs.

Mechanism of Action of TKIs

Broadly, tyrosine kinases play a pivotal role in modulating growth factor signaling.[2] When activated, these enzymes lead to increased tumor cell proliferation and growth, induce antiapoptotic effects, and promote angiogenesis and metastasis (Figure). When activated by somatic mutations, protein kinases play a role in initiating tumorigenesis as well. Tyrosine kinases are enzymes that catalyze the transfer of the γ phosphate group from adenosine triphosphate to target proteins and participate in diverse normal cellular regulatory processes. They can be divided into 2 subgroups: receptor tyrosine kinases and nonreceptor tyrosine kinases. The receptor tyrosine kinases are membrane-spanning cell surface proteins that comprise an extracellular N-terminal that binds to a ligand and a conserved, C-terminal region that autophosphorylates to create binding sites for phosphotyrosine-binding proteins. Binding of the ligand to the extracellular receptor results in autophosphorylation of the cytoplasmic domains to activate tyrosine kinase activity. Multiple cytoplasmic signaling pathways are then activated. Nonreceptor tyrosine kinases relay intracellular signals. Intracellular mediators in these pathways transduce signals from membrane receptors into the nucleus, which causes a variety of cellular processes—namely DNA synthesis and cell division, but also cell growth, migration, differentiation, and death.[3,4] In cancer cells, the C-terminal domain may be mutated so that even in the absence of a ligand, the kinases continue to be activated. TKIs, as their names imply, competitively bind or allosterically inhibit adenosine triphosphate to inhibit this signal transduction.[1]

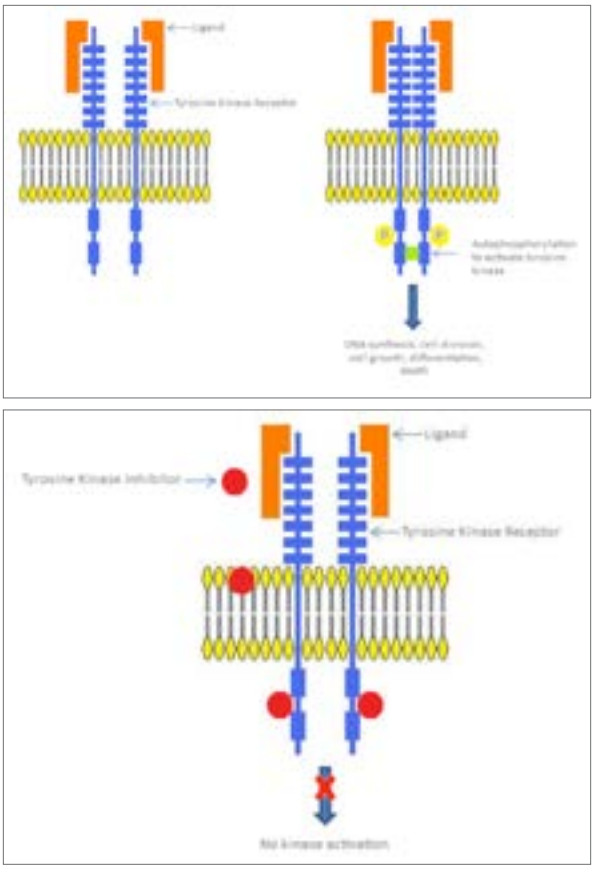

Figure. Tyrosine kinase inhibitors and their mechanism of action. The binding of a ligand to the receptor tyrosine kinase leads to activation of the intracellular kinase domain. The activation of the receptor requires the presence of adenosine triphosphate (ATP). The tyrosine kinase inhibitor penetrates into the cytoplasm and enters into competition with ATP for the ATP-binding pocket. The receptor can no longer activate its intracellular kinase domain when this occurs, preventing further downstream cell signaling.

Antiangiogenic Targets

HCC is a complex disease that has nearly every signaling pathway altered to cause tumorigenesis. This alteration is driven by mutations in oncogenes, tumor suppressor genes, and stability genes.[6] Hepatocarcinogenesis is thought to be a result of aberrant activation of different intracellular cell proliferation and angiogenesis pathways involving tyrosine kinase receptors, such as epidermal growth factor receptor (EGFR), VEGFR, PDGFR, fibroblast growth factor receptor (FGFR), hepatocyte growth factor (HGF)/c-mesenchymal-epithelial transition factor (c-Met), and insulin growth factor receptor (IGFR). These pathways activate various intracellular RAS/RAF/mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK), and phosphatidylinositol 3-kinase (PI3K)/Akt (Protein kinase B, PKB)/mammalian target of rapamycin (mTOR) signaling pathways.[7,8] HCC is a highly vascular tumor and the overexpression of both VEGF and VEGFR has been reported frequently. VEGF levels also correlate with microvessel density, angiogenic activity, tumor progression, metastasis, postoperative recurrence, and poorer prognosis.[9-11] Because HCC is a highly vascular tumor, the success seen with sorafenib is attributed to its inhibition of VEGF intracellular kinase pathway, and partly to the inhibition of the RAS/RAF/MEK/ERK mitogen-activated protein kinases at the level of RAF.

TKIs can target multiple receptors, owing to similarities in catalytic domains of FGFR, VEGFR, and PDGFR.[12] Although this decrease in specificity may lead to off-target effects and toxicities (namely rash and transfusion-reaction like symptoms), it may also allow for multiple sites of inhibition of different kinases.[13] Inhibition of more than 1 kinase may increase efficacy by disrupting redundant pathways.[12]

As a result of sorafenib's mortality benefit thought to be attributed to its antiangiogenic properties, the majority of HCC clinical trials are evaluating the efficacy of TKIs targeting angiogenesis pathways (Table 1).[13]

Table 1. Completed Phase 2 and 3 Studies Evaluating TKIs in Unresectable HCC

	Source	Phase	Year	Target Population	No. Pts	Study Arms	Primary Endpoint	OS	PFS	TTP
First-Line Studies										
	Llovet[1]	3	2008	Advanced HCC	299	Sorafenib	OS/TSP	10.7		5.5
					303	Placebo		7.9		2.8
	Cheng[37]	3	2009	Advanced HCC	150	Sorafenib		6.5		2.8
					76	Placebo		4.2		1.4
	Cheng[14]	3	2011	Advanced HCC	529	Sunitinib	OS	8.1	3.6	4.1
					544	Sorafenib		10	2.9	4
	Johnson[16]	3	2012	Advanced HCC	577	Brivanib	OS[a]	9.5		4.2
					578	Sorafenib		9.9		4.1
	Cainap[23]	3	2012	Advanced HCC		Linifanib	OS[a]	9.1		5.4
						Sorafenib		9.8		4
	Kaseb[27]	2	2012	Advanced HCC	59	Erlotinib+ bevacizumab	PFS at 16 weeks	13.7	64%[b]	
									7.2[c]	
	Abou-Alfa[28]	2	2010	Advanced HCC	47	Doxorubicin+ sorafenib	TTP	13.7	6	6.4
					49	Doxorubicin		6.5	2.7	2.8
Second-Line Studies										
	Llovet[21]	3	2012	Advanced HCC, progressed on or intolerant to sorafenib	263	Brivanib	OS	9.4		4.2
					132	Placebo		8.2		2.7
	Santoro[42]	2	2013	Advanced HCC, progressed on or intolerant to first-line therapy	71	Tivantinib	TTP			1.6[d]
					36	Placebo				1.4
	Verslype[47]	2	2012	Unresectable HCC		Cabozantinib	OS	15.1	4.2	

HCC, hepatocellular carcinoma; m, months; OS, overall survival; Pts, patients; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TSP, time to symptomatic progression; TTP, time to progression.

[a]Predefined noninferiority margins were not met.

[b]Percentage of PFS at 16 weeks.

[c]Median PFS.

[d]In MET-positive tumors vs placebo: TTP, 2.7 vs 1.4 months; OS, 7.2 vs 3.8 months.

Recently, 3 TKIs were tested against sorafenib in phase 3 studies. Sunitinib (Sutent, Pfizer) is a multitargeted TKI of VEGFR, PDGFR, c-KIT, and FLT-3. Although the phase 2 study did not show sunitinib to be superior to the treatment of historical controls, a first-line phase 3 study was initiated. It enrolled 1073 Child-Pugh class A patients—primarily from Asia—who had unresectable HCC, and compared sunitinib with sorafenib to test both noninferiority and superiority. The primary endpoint was median overall survival, which was 8 months for the sunitinib group vs 10 months for the sorafenib group (hazard ratio [HR], 1.31; 95% CI, 1.13-1.52; *P*=.0019).[14] The trial was stopped early by an independent data monitoring committee because of futility and safety concerns.

Brivanib, an inhibitor of VEGF and FGF, was studied in a phase 2 trial of 55 patients and showed a 6-month progression-free survival of 18.2% and a median overall survival of 10 months, which were comparable to previous results seen with sorafenib.[15] Despite the fact that brivanib did not show any superiority to historical controls, 2 separate phase 3 studies studying brivanib as first- and second-line therapy were initiated. The trial studying brivanib as first-line treatment followed 1155 patients with advanced HCC who had not received prior systemic therapy. It did not meet criteria for noninferiority to sorafenib; the primary endpoint of overall survival was 9.9 months for sorafenib treatment vs 9.5 months for brivanib (HR, 1.06; 95% CI, 0.93-1.22; *P*=.3730).[16] Brivanib was also investigated as second-line therapy to address those HCC patients who progressed while on sorafenib or who were unable to tolerate sorafenib treatment. It was considered a promising second-line therapy, owing to preclinical models suggesting that phenotypic resistance to VEGFR inhibition could activate VEGF-independent angiogenic signals by way of the FGF family. There was also evidence from genomic and functional studies showing that members of the FGF family were oncogenic drivers in HCC.[17-19]

A phase 2 study of brivanib was initially conducted in 46 patients who had failed previous antiangiogenic therapy.[20] This resulted in a median overall survival of 9.79 months, which prompted a phase 3 study comparing brivanib plus best supportive care (BSC) with placebo plus BSC. Among 395 randomized patients, 87% had disease progression while on sorafenib, 59% had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 0, 72% had vascular invasion/extrahepatic spread, 92% had Child-Pugh class A liver function, and 86% of patients had Barcelona Clinic Liver Cancer (BCLC) stage C disease. Unfortunately, the study did not meet its primary endpoint of median overall survival (9.4 months in the brivanib group vs 8.2 months with placebo; *P*=.3307).[21] However, significant improvement in time to progression ([TTP], 4.2 months vs 2.7 months, respectively; *P*<.001) and response to treatment (12% vs 2%, respectively; *P*=.0030) were observed.

Linifinib, a potent TKI against PDGF and VEGF, was found in a phase 2 study of 44 patients to yield a median overall survival of 9.7 months.[22] A first-line phase 3 study of 1035 patients (median age of 60 years, 68% Asian, 65% ECOG PS 0, 49% hepatitis B virus (HBV), 70% vascular invasion or extrahepatic spread) failed to show an improvement in survival with linifinib over sorafenib. The median overall survival was 9.1 months for linifanib (95% CI, 8.1-10.2) vs 9.8 months for sorafenib (HR, 1.046; 95% CI, 0.896-1.221).[23] Adverse events leading to discontinuations, dose interruptions, and reductions were more frequent in the linifinib arm vs the sorafenib arm (*P*<.001).

Combination Therapies

Although preclinical studies suggested that the newer TKIs would be very potent and targeted therapies, these agents have not been shown to be superior to sorafenib. Newer therapeutic strategies have attempted to target angiogenesis signaling at multiple sites. Combination therapies that hit pathways involved in angiogenesis have undergone evaluation as first- and second-line treatments for HCC. A phase 2 trial tested the combination of the EGFR-TKI erlotinib (Tarceva, Astellas Pharma Inc) and the VEGFA monoclonal antibody bevacizumab (Avastin, Genentech) in treatment-naive patients with advanced HCC. VEGF and EGF pathways share common downstream signals, and preclinical studies have shown direct or indirect proangiogenic effects of EGFR signaling.[24-26] The progression-free survival at 16 months was 64% (95% CI, 51-76), with a median overall survival of 13.7 months (95% CI, 9.6-19.7), and a median progression-free survival of 7.2 months (95% CI, 5.6-8.3).[27] Currently, a randomized phase 2 trial comparing bevacizumab and erlotinib vs sorafenib is ongoing (NCT00881751).

Another approach to combination therapy is to add TKIs to existing chemotherapeutic agents, such as doxorubicin. A rationale for this approach stems in part from the lack of improvement in outcomes seen after specific targeting of angiogenic pathways. Cancers may minimize dependency on angiogenesis in order to survive. A randomized, double-blind, phase 2 study in patients with advanced HCC and Child-Pugh grade A cirrhosis showed that the combination of doxorubicin and sorafenib conferred a significant improvement in median overall survival of 13.7 months, compared with 6.5 months for placebo (*P*=.006).[28] This combination may be efficacious because of the theorized synergy between the 2 drugs, namely the dismantling of the Ask1-RAF dimer, which reverts Ask1 back to the cell's cytoplasm, thus helping doxorubicin's apoptotic effect.[29] At this time, a phase 3 study sponsored by the National Cancer Institute is comparing combination sorafenib and doxorubicin therapy with sorafenib alone in patients with unresectable HCC who have not received prior systemic therapy (NCT01015833).

Combination therapy with sorafenib plus locoregional therapy such as transcatheter arterial chemoembolization (TACE) has also been investigated. The SPACE (Sorafenib or Placebo in Combination With Transarterial Chemoembolization for Intermediate-stage HCC) trial studied the effects of sorafenib plus TACE vs sorafenib alone.[30] A total of 307 patients with intermediate-stage HCC with Child-Pugh class A status were randomized to receive sorafenib 400 mg twice daily or matching placebo, with treatment cycles repeated every 4 weeks until untreatable disease progression. TACE was performed on day 1 of cycles 1, 3,

7, 13, and every 6 cycles thereafter. The primary endpoint was time to radiologic progression, with a median TTP of 169 days and 166 days in the sorafenib and placebo groups, respectively. The HR for TTP was 0.797 (95% CI, 0.588-1.080; *P*=.072). Secondary endpoints of overall survival, time to vascular invasion/intrahepatic spread, and time to untreatable progression did not meet significance. Unfortunately, efforts to combine sorafenib with locoregional therapies have not been fruitful.

Heterogeneity of HCC

Although newer TKIs have been studied, they have not been shown to be superior to sorafenib. Alternative TKIs confer a maximum median survival of 10 months.[31] There have been several theories attempting to explain this apparent ceiling in efficacy. A potential reason may be explained by the genetic heterogeneity of HCC. Cleary and associates conducted a combined analysis of whole-exome sequencing from 158 surgically resected tumors, and demonstrated that no single protein kinase has more than a 5% frequency in HCC.[32-37] This scarcity of uniform kinase mutations is likely a reason why a dramatic response to TKIs seen in other cancers is not noted in HCC.

Variable response rates to therapy depending on the etiology of HCC (HBV, hepatitis C virus [HCV], alcohol-induced, metabolic disease) also underscore the heterogeneous biology of HCC. In the Asia-Pacific Study, which compared sorafenib with placebo, the median overall survival favored sorafenib treatment over placebo (6.5 vs 4.2 months; HR, 0.68; 95% CI, 0.5-0.93; *P*=.14).[38] In that study, the most common underlying liver disease etiology was HBV infection (73%). This is in contrast to SHARP (Sorafenib HCC Assessment Randomized Protocol Trial) , where the overall survival of patients on sorafenib was substantially higher (10.7 months).[1] In a subgroup analysis of the SHARP trial, there was a median overall survival of 15 months in patients with HCV vs 9.7 months in patients with HBV, which led to the hypothesis that sorafenib has anti-HCV activity.[39] Sorafenib, which targets RAF, may be efficacious in patients with HCV because of the association between HCV-1 core protein and an increase in RAF kinase activity.[40] On the other hand, a study found that sorafenib has a marginal effect on the HCV viral load in patients with HCV-associated HCC.[41] A difference in overall survival based on region was again seen in the phase 3 trial of sunitinib vs sorafenib.[14] In this case, patients were not stratified based on disease cause but by region; the median overall survival was 18.3 months for patients living outside of Asia compared with 7.9 months for those living in Asia. Although the Asia-Pacific Study initially suggested that differences in disease etiology may be the most significant reason for the discrepancy in survival, it is more likely that the true reason is a combination of several different factors that deserve additional investigation.

MET Inhibition

A new area of interest in personalized therapy is targeting the MET receptor tyrosine kinase, which is encoded by the MET proto-oncogene and plays a role in tumor development and metastases.[42] Tissue c-MET overexpression has been shown to have prognostic value in relation to tumor grade, portal vein invasion or thrombosis, intrahepatic metastases, tumor recurrence, and overall survival.[43] One large retrospective study of 194 patients with HCC who had received prior treatment with partial hepatectomy or microwave ablation showed that increased c-MET expression was associated with worse survival.[44] Tivantinib (ARQ 197) is an oral TKI that preferentially inhibits growth and causes apoptosis in tumor cell lines expressing MET. Sensitivity to tivantinib was confirmed in HCC lines as well as antitumor activity in murine models in various tumors.[45,46] A randomized phase 2 study evaluating second-line treatment with tivantinib vs placebo showed that in all patients, TTP was marginally improved in the tivantinib arm compared with patients who received placebo (1.6 vs 1.4 months; *P*=.04).[42] However, the difference was notably more marked in those patients expressing MET-positive tumors (>50% of tumor cells expressing MET positivity by immunohistochemistry). There were significant improvements in median TTP (2.7 vs 1.4 months; HR, 0.43; 95% CI, 0.19-0.97; *P*=.03) and median overall survival (7.2 vs 3.8 months; HR, 0.38; 95% CI, 0.18-0.81; *P*=.01).[42] Currently, a phase 3 study is comparing tivantinib vs placebo in patients with MET diagnostic-high inoperable HCC who have failed 1 prior systemic therapy (NCT01755767).

Cabozantinib, an oral TKI that inhibits both MET and VEGFR-2, has been assessed as a second-line therapy for HCC in a phase 2 randomized discontinuation trial.[47] Patients were treated based on their response at 12 weeks. Patients with an evident response continued on open-label cabozantinib, patients with stable disease were randomly assigned to cabozantinib or placebo, and those with progressive disease discontinued cabozantinib. The primary endpoint was median overall survival for patients who were randomly assigned. In the 41 patients studied, median progression-free survival was 4.4 months and median overall survival was 15.1 months. The hope is that dual inhibition of angiogenesis pathways and the MET pathway will confer a more potent benefit. As with tivantinib, a randomized trial for cabozantinib is in its planning stages. Continued study into the genetic alterations of HCC will be important in order to identify more targets that may benefit certain subsets of patients with HCC. As we have already begun to see, identifying patients with the MET proto-oncogene holds promise for those who display increased c-MET expression, which has portended a poor prognosis.

Conclusion

Additional research will be necessary in order to pinpoint valuable targets in HCC. A scarcity of uniform kinase mutations may be the reason why HCC has not responded in dramatic form when compared with other cancer types.[48] As such, developing customized therapy for various subsets of patients with HCC is essential for the future.

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