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REVIEW

Sorafenib in advanced hepatocellular carcinoma: current status and future perspectives

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Abstract: The approval of sorafenib, a multikinase inhibitor targeting primarily Raf kinase and the vascular endothelial growth factor receptor, in 2007 for treating advanced hepatocellular carcinoma (HCC) has generated considerable enthusiasm in drug development for this difficult-to-treat disease. However, because several randomized Phase III studies testing new multikinase inhibitors failed, sorafenib remains the standard of first-line systemic therapy for patients with advanced HCC. Field practice studies worldwide have suggested that in daily practice, physicians are adopting either a preemptive dose modification or a ramp-up strategy to improve the compliance of their patients. In addition, accumulating data have suggested that patients with Child–Pugh class B liver function can tolerate sorafenib as well as patients with Child–Pugh class A liver function, although the actual benefit of sorafenib in patients with Child–Pugh class B liver function has yet to be confirmed. Whether sorafenib can be used as an adjunctive therapy to improve the outcomes of intermediate-stage HCC patients treated with transcatheter arterial chemoembolization or early-stage HCC patients after curative therapies is being investigated in several ongoing randomized Phase III studies. An increasing number of studies have reported that sorafenib exerts "off-target" effects, including the modulation of signaling pathways other than Raf/MEK/ERK pathway, nonapoptotic cell death mechanisms, and even immune modulation. Finally, although sorafenib in combination with chemotherapy or other targeted therapies has the potential to improve therapeutic efficacy in treating HCC, it also increases toxicity. Additional clinical studies are warranted to determine useful sorafenib-based combinations for the treatment of advanced HCC.

Keywords: HCC, multikinase inhibitor, advanced stage, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related deaths worldwide.[1] Patients diagnosed in East and Southeast Asia account for more than 70% of the global burden of HCC, and the incidence of HCC in Europe and North America is also increasing. The major etiological factors of HCC are chronic hepatitis B virus (HBV) infection in most Asian countries, chronic hepatitis C virus (HCV) infection in Japan and Western countries, and alcoholism in Western countries.[2,3] Recent studies suggest that nonalcoholic fatty liver disease, especially the aggressive form, nonalcoholic steatohepatitis, may be associated with an increased risk of HCC.[2,4] Although localized HCC can be cured through resection, liver transplantation, or local ablation, only a minority of patients are eligible for these options at the time of their diagnosis.[2,3] Most HCC patients eventually succumb to metastatic or locally advanced HCC.

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The approval of sorafenib for treating advanced HCC in 2007 represented a milestone in the history of HCC therapeutics. Sorafenib is a multikinase small-molecule inhibitor that targets several signaling pathways, especially Raf kinase and the vascular endothelial growth factor receptor (VEGFR).[5,6] Two large placebo-controlled randomized Phase III trials, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study conducted in Europe and the United States and the Sorafenib Asia–Pacific (Sorafenib-AP) study conducted in China, South Korea, and Taiwan, unequivocally underscored the survival benefit of sorafenib in patients with advanced HCC.[7,8] Reduction in mortality risk was similar in both studies, and overall survival (OS) improved from 7.9 to 10.7 months in the SHARP study and from 4.2 to 6.5 months in the Sorafenib-AP study.

Sorafenib remains the standard of care: 7 years on

The success of sorafenib has generated renewed enthusiasm in exploring new drugs for HCC. However, as summarized in Table 1, none of these multikinase inhibitors or a sorafenib-based combination with another targeted agent have shown superior efficacy to sorafenib alone.[9–12]

Sunitinib, a multikinase inhibitor that primarily targets VEGFR and platelet-derived growth factor receptor (PDGFR), is a potent antiangiogenic agent. In an open-label, randomized Phase III study, 1,074 patients with advanced HCC were randomized to receive either sunitinib 37.5 mg once per day or sorafenib 400 mg twice per day.[9] The median OS was significantly lower in the sunitinib arm than in the sorafenib arm (7.9 versus [vs] 10.2 months). However, a post hoc analysis revealed that the median OS in the sunitinib and sorafenib arms was similar among HBV-infected patients (7.6 vs 8.0 months), but was significantly different among HCV-infected patients (9.2 vs 17.6 months). In addition, sunitinib was associated with more frequent and severe adverse events (AEs).

Like sunitinib, linifanib (ABT-869) is another multikinase inhibitor that targets primarily VEGFR and PDGFR. In an open-label, randomized Phase III study, 1,035 patients with advanced HCC were randomized to receive either linifanib 17.5 mg per day or sorafenib 400 mg twice per day.[10] Although linifanib appeared to yield a higher response rate

Table 1 Published Phase III studies using sorafenib as first-line systemic therapy for advanced HCC

Reference	Key eligibility criteria	Treatment arm	Patient number	Median TTP (months)	HR (95% CI) in TTP	Median OS (months)	HR (95% CI) in OS
Sorafenib compared with placebo							
Llovet et al,[7] (SHARP) 2008	Pathologic diagnosis Child–Pugh class A	Sorafenib vs	299	5.5	0.69 (0.55–0.87)	10.7	0.69 (0.55–0.87)
	ECOG PS =0–2	placebo	303	2.8	$P<0.001$	7.9	$P<0.001$
Cheng et al,[8] (Sorafenib-AP) 2009	Pathologic diagnosis Child–Pugh class A	Sorafenib vs	150	2.8	0.57 (0.42–0.79)	6.5	0.68 (0.50–0.93)
	ECOG PS =0–2	placebo	76	1.4	$P=0.0005$	4.2	$P=0.014$
Sorafenib compared with other multikinase inhibitors							
Cheng et al,[9] 2013	Pathologic diagnosis Child–Pugh class A	Sunitinib vs	530	4.1	1.13 (0.98–1.31)	7.9	1.30 (1.13–1.50)
	ECOG PS =0–1	sorafenib	544	3.8	$P=0.8312$* $P=0.3082$**	10.2	$P=0.990$* $P=0.0014$**
Cainap et al,[10] 2013	Pathologic diagnosis Child–Pugh class A	Linifanib vs	1,035 (1:1 randomization)	5.4	N/A	9.1	1.046 (0.896–1.221)#
	ECOG PS =0–1	sorafenib		4.0		9.8	
Johnson et al,[11] (BRISK-FL) 2013	Pathologic diagnosis Child–Pugh class A	Brivanib vs	577	4.2	1.01 (0.88–1.16)	9.5	1.06† (0.93–1.22)
	ECOG PS =0–1	sorafenib	578	4.1	$P=0.8532$	9.9	$P=0.3730$
Sorafenib compared with sorafenib-based combination							
Zhu et al,[12] (SEARCH) 2012	Pathologic diagnosis Child–Pugh class A	Sorafenib + erlotinib vs	362	3.2	1.135 (0.944–1.366)	9.5	0.929 (0.781–1.106)
	ECOG PS =0–1	sorafenib	358	4.0	$P=0.91$	8.5	$P=0.204$

Notes: *One-sided *P* values calculated for OS and TTP, defined in the protocol; **two-sided *P* values; #not reaching predefined superiority or noninferiority OS boundaries; †data derived from the per-protocol population (n=1,150); the data was similar to OS in the intention-to-treat population (HR, 1.07; 95.8% CI, 0.94 to 1.23; $P=0.3116$).
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HR, hazard ratio; N/A, not available; OS, overall survival; SEARCH, Sorafenib and Erlotinib, a rAndomized tRial protoCol for the treatment of patients with Hepatocellular carcinoma; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol; Sorafenib-AP, Sorafenib-Asia–Pacific; TTP, time to progression.

(13.0% vs 6.9%) and a longer median time to tumor progression (TTP) (5.4 vs 4.0 months), no significant difference in OS between the linifanib and sorafenib arms was observed. The median OS was 9.1 months in the linifanib arm and 9.8 months in the sorafenib arm.

Brivanib is a multikinase inhibitor that targets primarily the VEGFR and fibroblast growth factor receptor (FGFR). The FGFR pathway is a key angiogenic signaling pathway that plays a critical role in the development of the drug resistance of cancer cells to VEGF-targeting therapies.[13–15] In a double-blind, multinational Phase III (BRISK-FL) study, 1,155 patients with advanced HCC were randomized to receive either brivanib 800 mg once per day or sorafenib 400 mg twice per day.[11] The median OS was 9.5 months in the brivanib arm and 9.9 months in the sorafenib arm. The primary endpoint of OS noninferiority among patients treated with brivanib compared with those treated with sorafenib was not met (hazard ratio [HR] =1.06; 95% confidence interval [CI] =0.93–1.22), based on the prespecified margin (upper CI limit for HR ≤1.08). Brivanib exhibited an acceptable safety profile, but was less well-tolerated than sorafenib. Brivanib yielded higher rates of grade 3 and 4 toxicities for hypertension, fatigue, and hyponatremia, and higher rates of drug discontinuation because of AEs.

A double-blind Phase III study (SEARCH [Sorafenib and Erlotinib, a rAndomized tRial protoCol for the treatment of patients with Hepatocellular carcinoma] trial) investigated the combination of sorafenib and erlotinib, a tyrosine kinase inhibitor targeting the epidermal growth factor receptor (EGFR).[12] A total of 720 patients were randomized to receive either sorafenib 400 mg twice per day plus erlotinib 150 mg once per day or sorafenib plus a placebo. Sorafenib plus erlotinib did not prolong either TTP (3.2 vs 4.0 months) or OS (9.5 vs 8.5 months) compared with sorafenib plus placebo. The median treatment duration was shorter (2.8 vs 4.0 months), and the withdrawal rate after one treatment cycle was greater (34.0% vs 23.8%) in the sorafenib plus erlotinib arm than in the sorafenib plus placebo arm.

Importantly, there might be a stage migration toward earlier patient enrollment in recently reported Phase III trials (Table 2). In the Phase III study comparing sunitinib with sorafenib, the median OS in the sorafenib arm was 8.8 months among Asian patients and 15.1 months among non-Asian patients.[9] These OS times were longer than those observed in the pivotal Sorafenib-AP study (median OS, 6.5 months for Asian patients) and SHARP study (median OS, 10.7 months for non-Asian patients). Again, in the Phase III study comparing brivanib with sorafenib, the median OS in the sorafenib arm was 8.9 months among Asian patients and 11.8 months among non-Asian patients.[11] The improved survival of the sorafenib arm in recent studies could be attributed to the stage migration of the patients; in other words, instead of enrolling end-stage advanced HCC patients, investigators are increasingly enrolling patients who exhibit more favorable performance statuses and less extensive diseases. Furthermore, improved skill and experience in managing the categorical toxicities of sorafenib, as well as active antiviral therapy for treating underlying hepatitis, may also play a role in improving OS. In general, the median OS in the sorafenib arm is generally around 9 months in Asian patients with advanced HCC and 12 months in Western patients. This observation must be taken into consideration for future first-line Phase III trials of systemic therapy in treating advanced HCC.

Mechanisms of action: conventional and beyond

Sorafenib, a bi-aryl urea, was initially developed as a Raf kinase inhibitor, with a potent IC_{50} of 6 nM against Raf1 kinase in an in vitro kinase assay. Sorafenib also potently inhibited B-Raf kinase, proangiogenic receptor tyrosine

Table 2 Comparison of overall survival times in advanced HCC patients receiving first-line sorafenib treatment in randomized Phase III studies

Reference	Treatment	Total patient number	Asian: non-Asian (%)	Median overall survival (months)		
				Overall population	Asian subgroup	Non-Asian subgroup
Llovet et al,[7] 2008	Sorafenib vs placebo	602	0:100	10.7	–	10.7
Cheng et al,[8] 2009	Sorafenib vs placebo	226	100:0	6.5	6.5	–
Cheng et al,[9] 2013	Sunitinib vs sorafenib	1,074	77:23	10.2	8.8	15.1
Cainap et al,[10] 2013	Linifanib vs sorafenib	1,035	68:32	9.8	N/A	N/A
Johnson et al,[11] 2013	Brivanib vs sorafenib	1,155	62:38	9.9	8.9	11.8
Zhu et al,[12] 2012	Sorafenib + erlotinib vs sorafenib	720	N/A	8.5	N/A	N/A

Abbreviations: N/A, not available; vs, versus; HCC, hepatocellular carcinoma.

kinases, including VEGFR1/2/3 and PDGFRβ, and other receptor tyrosine kinases involved in tumorigenesis (c-Kit, Flt-3, and RET) in vitro, with IC_{50}s ranging from 20 to 90 nM.[5,6] In preclinical studies, sorafenib inhibited proliferation and induced apoptosis in cultured HCC cells, and suppressed the growth of HCC xenografts in immunocompromised mice.[16] In the immunocompromised mice, growth suppression was accompanied by decrease in microvessel areas and increased tumor cell apoptosis. These data suggest that the antitumor activity of sorafenib is mediated by an indirect antiangiogenic effect on the microenvironment and a direct effect on cancer cells.[16]

Recent studies have explored other possible mechanisms of action through which sorafenib affects HCC. Sorafenib was found to affect multiple cell signaling pathways other than the Raf/MEK/ERK pathway, and to induce multiple mechanisms leading to apoptosis or other types of cell death in tumor cells. Furthermore, recent studies have suggested that sorafenib has "immune-modulatory" functions. Table 3 summarizes the key findings of these studies.[16–40]

Sorafenib, a small molecule that inhibits multiple protein kinases, can affect the intricate balance of the complex signaling network in cells. For example, inhibition of the Raf/MEK/ERK pathway can activate other prosurvival signaling pathways, such as the PI3K/AKT and transforming growth factor α/EGFR pathways, thus leading to sorafenib resistance.[21,22,25] In preclinical studies, combinations of sorafenib and inhibitors of these compensatory prosurvival signaling pathways exhibited improved therapeutic effects. Some promising preclinical findings have been translated into clinical trials. However, the first Phase III study testing the combination of sorafenib and an EGFR inhibitor (SEARCH trial) in advanced HCC patients was unsuccessful.[12]

Investigating the off-target effects of sorafenib in HCC cells may lead to the discovery of new therapeutic targets. Chen et al found that downregulation of phosphorylated signal transducer and activator of transcription 3 (p-STAT3) was the key mechanism of action of sorafenib.[17] This group of investigators continued to demonstrate that sorafenib targets Src homology region 2 domain-containing phosphatase 1 and increases its phosphatase activity, leading to the downregulation of p-STAT3.[18,19]

In addition, recent studies have suggested that sorafenib might have immune-modulatory effects. Sorafenib could affect the quantity and quality of immune cells involved in antitumor immunity, including effector T cells, regulatory T cells, natural killer cells, and tumor-associated macrophages.[34–40] However, the results of these studies were not always consistent, and most of the findings have not yet been validated in patients with HCC.

Overall, the increasing number of mechanistic studies on sorafenib has enhanced our understanding of the intricate interplay between prosurvival and prodeath signaling within tumor cells as well as the complex interaction between tumor cells and host immunity within the tumor microenvironment.

Prescription of sorafenib: preemptive dose modification and ramp-up

In the pivotal SHARP and Sorafenib-AP studies, the rate of dose interruption among patients treated with sorafenib was 44%.[7,8] The common toxicities leading to dose interruption were diarrhea, hand–foot skin reaction, fatigue, and skin rash/desquamation. These data suggest that a substantial number of advanced HCC patients might not be able to tolerate the standard dose of sorafenib.

An observational study of 54 Japanese patients with Barcelona-Clinic Liver Cancer (BCLC) stage C and B diseases treated with the standard dose of sorafenib reported that 83% of the patients required at least one dose reduction, and 44% of the patients underwent the first dose reduction within the first 2 weeks of treatment.[41] Another observational study of 116 patients treated with the standard dose of sorafenib in Italy reported that 62 patients (53%) required dose reduction or temporary interruption.[42] A large field practice observational study in Italy (SOFIA [SOraFenib Italian Assessment] study) enrolled 296 advanced HCC patients from six referral centers.[43] Dose reduction of sorafenib was required in 54% of the patients, and treatment interruption because of treatment-related AEs was observed in 40% of the patients. Consequently, only 46% of the patients received the full dose of sorafenib over the entire treatment period, and 26% of the patients received a half dose of sorafenib for more than 70% of the treatment period. Patients who received a half dose of sorafenib for more than 70% of treatment period had significantly longer treatment duration (median 6.8 vs 3 months) and significantly longer OS (median 21.6 vs 9.6 months) than other patients.[43] These studies suggested that dose modification and/or dose interruption are common in HCC patients treated with the standard dose of sorafenib. The results of the SOFIA study implied that timely dose modification may lead to an increased treatment duration and an improved patient outcome.

The "preemptive dose modification" strategy, in which dose modification is implemented earlier than recommended

Table 3 Published studies exploring mechanisms of action of sorafenib in HCC

Reference	Key finding	Mechanistic insight or translational implication
On cellular signaling pathways		
Chen et al,[17] 2010 and Tai et al,[18] 2011	Downregulation of p-STAT3	Sorafenib inhibited HCC via a kinase-independent mechanism; downregulation of p-STAT3 was mediated by upregulating SHP-1 (a phosphatase) activity.[17,18]
Ou et al,[20] 2010	Activation of JNK	Activation of JNK, which contributes to induction of GADD45β, preferentially occurred in sorafenib-sensitive HCC cells. Sorafenib-induced JNK activation was independent of Raf/MEK/ERK.
Gedaly et al,[21] 2010	Activation of PI3K/AKT pathway	Combination of sorafenib and a dual PI3K/mTOR inhibitor produced a synergistic antitumor effect against HCC in vitro and in vivo.[21,22]
Lanchemayer et al,[23] 2012	Downregulation of WNT signaling and β-catenin protein	Two different Wnt-related molecular classes (CTNNB1 and Wnt-TGFβ) were identified, accounting for half of all HCC patients. Sorafenib could modulate β-catenin/Wnt signaling in experimental models that harbor the CTNNB1 class signature.
Liu et al,[24] 2012	Inhibition of hypoxia-induced HIF-1α protein expression	This downregulation of HIF-1α was associated with downregulation of mTOR/p70S6K/4E-BP1 and ERK. Sorafenib also decreased VEGF protein expression.
Zhao et al,[25] 2014	Activation of TGFα/EGFR pathway	Hypoxic HC cells contributed to the activation of TGFα/EGFR pathway, upregulation of HIF-2α, and resistance to sorafenib.
On cell death mechanisms		
Liu et al,[16] 2006	Downregulation of Mcl-1	An ERK-independent mechanism contributed to increased apoptosis in HCC cells. In another study, the combination of sorafenib and ABT-737, which could inactivate Bcl-xL, led to strong suppression of HCC cells.[26]
Ou et al,[27] 2009	Increasing Bim protein expression	Bim activation mediated the synergistic antitumor effect of sorafenib and MEK inhibitor in HCC cells.
Chiou et al,[28] 2009	Increasing production of ROS	A mitochondria-dependent oxidative stress mechanism mediated the apoptosis induced by sorafenib in HepG2 cells. In another study, serum levels of advanced oxidative protein products were increased in HCC patients treated with sorafenib.[29]
Ou et al,[20] 2010	Induction of GADD45β	Induction of GADD45β, through activation of JNK, contributed to the sorafenib-induced apoptosis in HCC cells.
Galmiche et al,[30] 2010	Activation of BAD	Sorafenib, via an ERK-independent manner, increased BAD expression and prevented its inhibitory phosphorylation in HCC cells.
Shi et al,[31] 2011	ER stress-induced cell death	Sorafenib, via an MEK/ERK-independent manner, induced apoptosis and autophagy. The ER stress-induced cell death was attenuated by autophagy activation. Inhibition of autophagy enhanced sorafenib-induced cell death.
Li et al,[32] 2012	Downregulation of c-IAP1	Sorafenib decreased the protein expression level of c-IAP1 by targeting the internal ribosome entry site within the c-IAP1 mRNA.
Sonntag et al,[33] 2014	Increasing expression of PUMA	Sorafenib-mediated apoptosis in murine hepatoma cells, not in syngeneic mouse primary hepatocytes, was associated with the expression of PUMA.
On immune cell function and immune microenvironment		
Cao et al,[34] 2011	Decreasing the suppressive immune cell populations (Treg and MDSC)	Treg and MDSC were increased in the spleens and bone marrows of the BALB/c mice with liver hepatoma. Sorafenib treatment inhibited HCC cell growth in mice, and significantly decreased the suppressive immune cell populations.
Cabrera et al,[35] 2013	Immune modulation on effector CD4 and Treg function	In T cells cultured from patients with HCC, subpharmacologic doses of sorafenib (<3 μM) increased effector T cell activation while blocking Treg function, and pharmacologic doses of sorafenib (6~12 μM) decreased effector T cell activation.
Wang et al,[36] 2013	Decreasing tumor-infiltrated Treg cells	In tumor infiltrated mononuclear cells from 19 HCC patients, tumor-infiltrated regulatory T cells were decreased significantly and TGF-β signal pathways were downregulated after sorafenib.
Zhang et al,[37] 2013	Reducing the number and function of NK cells	In a mouse model, suppression of NK cells by sorafenib contributed to prometastatic effects in HCC. The study suggests immunotherapeutic approaches activating NK cells may enhance the efficacy of sorafenib in HCC patients.
Sprinzl et al,[38] 2013	Triggering activation of hepatic NK cells	In a mouse model, sorafenib triggered proinflammatory activity of tumor-associated macrophages and induced antitumor NK cell responses in a cytokine- and NF-κB-dependent fashion.

(*Continued*)

Table 3 (*Continued*)

Reference	Key finding	Mechanistic insight or translational implication
Chen et al,[39] 2014	Enhancing functions of tumor-specific effector T cells	In a mouse model, sorafenib enhanced functions of effector T cells, and decreased the number and functions of PD-1-expressing CD8+ T cells and Tregs in a tumor microenvironment.
Chen et al,[40] 2014	Increasing Gr-1+ myeloid cell infiltration	In a mouse model, sorafenib intensified tumor hypoxia, which then increased SDF1α expression, Gr-1+ myeloid cell infiltration, and subsequently tumor fibrosis. Combination of CXCR4 inhibitor or depletion of Gr-1+ cells improved the therapeutic efficacy of sorafenib.

Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; BAD, Bcl-2-associated death promoter; Bcl-xL, B-cell lymphoma-extra large; CXCR4, C-X-C chemokine receptor type 4; IAP, the inhibitors of apoptosis; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GADD45β, growth arrest DNA damage induced gene 45β; HCC, hepatocellular carcinoma; HIF, hypoxia-inducing factor; JNK, c-Jun NH2-terminal kinase; MDSC, myeloid-derived suppressor cell; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NK cells, natural killer cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p-STAT3, phosphorylated signal transducer and activator of transcription 3; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PUMA, p53 upregulated modulator of apoptosis; ROS, reactive oxidative species; SDF1α, stromal-derived factor 1α; SHP-1, Src homology region 2 domain-containing phosphatase-1; TGF, transforming growth factor; Treg, regulatory T cell; WNT, wingless-related integration site.

in the package insert, has become common practice. The dose modification rule for sorafenib as listed in the package insert requests treatment interruption upon grade ≧2 dermatological toxicities, grade ≧3 hematological toxicities, or grade ≧4 other nonhematological toxicities; the treatment can be resumed with dose modification when the toxicities recover to grade 0 or 1.[7,8] This dosing guideline often leads to an overshooting of toxicities and treatment interruption. Furthermore, it has been shown that interruption of antiangiogenic therapy may induce a "rebound" phenomenon; that is, rapid tumor growth upon drug withdrawal.[44] Therefore, it is reasonable that physicians tend to follow up with their patients frequently and reduce the dose of sorafenib preemptively to prevent overshooting of toxicities and treatment interruption.

Alternatively, a "ramp-up" strategy, which involves administering sorafenib to high-risk patients at a reduced dose initially and escalating the dose only when the toxicity is acceptable,[45] has also become popular in clinical practice. The GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) study was conducted to evaluate the safety of sorafenib in real-world practice.[46] Of the 1,571 patients eligible for safety analysis, 22% were treated with an initial dose of 400 mg per day. In a single-institute-based retrospective study conducted in Japan, 38 of 96 (40%) HCC patients were treated with sorafenib at the initial dose of 400 mg per day.[47] In a community-based study conducted in Canada, 66 of 99 (66%) HCC patients were treated with sorafenib at the initial dose of 400 mg per day.[48]

Overall, these observational studies have indicated that sorafenib prescription, either starting with a reduced dose (ie, "ramp-up" strategy) or earlier dose modification, is associated with improved patient compliance[45,48] and noninferior or improved OS.[43,45,47–49]

Indications for sorafenib: later and earlier

According to the pivotal SHARP and Sorafenib-AP studies, sorafenib is indicated for advanced-stage HCC patients with good liver function reserves (ie, Child–Pugh class A). Whether sorafenib also plays a role in patients with impaired liver function (ie, Child–Pugh class B) (Table 4) as well as in earlier stages, including BCLC stage A and stage B, is being explored.

Advanced HCC with impaired liver function reserve

In the first Phase II clinical trial of sorafenib in advanced HCC, reported by Abou-Alfa et al, 38 (28%) of the 136 patients enrolled had Child–Pugh B liver function reserve.[50,51] The median treatment duration of sorafenib for Child–Pugh class B patients was 1.8 months, and their median OS was 3.2 months. The incidences of sorafenib-related AEs, including hand–foot skin reaction, fatigue, and diarrhea, were similar in Child–Pugh class B and Child–Pugh class A patients. However, grade 3 or 4 hyperbilirubinemia, ascites, and encephalopathy were more frequently observed in Child–Pugh class B patients than in class A patients. These liver-related AEs were likely the consequence of deterioration of the underlying hepatic condition in Child–Pugh class B patients. No significant difference in the pharmacokinetic profiles of sorafenib, including the area under the curve and peak concentration values, was observed between Child–Pugh class B patients and Child–Pugh class A patients.[51]

In the study reported by Pressiani et al, 63 (21%) patients with advanced HCC were classified as Child–Pugh class B.[52,53] The median treatment duration of sorafenib and the median OS for Child–Pugh class B patients were 1.9 months and 3.8 months, respectively.[52] The median daily doses did not differ significantly between patients with Child–Pugh class A

and class B liver function (744 and 762 mg). The type and frequency of AEs were similar in the two patient groups; however, grade 3 or 4 cachexia and liver failure were more frequently observed in Child–Pugh class B patients than in class A patients.[52]

Of the 120 consecutive HCC patients treated with sorafenib at a single institute in France, 18 patients with Child–Pugh class B liver function were, in a 1:3 ratio, matched to patients with Child–Pugh class A liver function in terms of age, performance status, tumor numbers and sizes, portal vein thrombosis, and serum alpha-fetoprotein levels.[54] No significant difference in the mean dose intensity of sorafenib was noted between Child–Pugh class B and Child–Pugh class A patients. The frequencies of all-grade and grade 3 or 4 drug-induced AEs were similar in the two patient groups. Child–Pugh class B patients tended to have a shorter median duration of treatment (2.3 vs 4.3 months) and a poorer OS (4.5 vs 10 months) than did class A patients.[54]

In the second interim analysis of the GIDEON study, 367 of the 1,571 patients were classified as Child–Pugh class B.[46] The median duration of sorafenib treatment was approximately 2.0 months.[46] The median daily doses (680 mg vs 721 mg) of sorafenib, drug-related all-grade AEs (67% vs 63%), and drug-related grade 3 or 4 AEs (24% vs 22%) were similar in Child–Pugh class A and class B patients. The rate of drug-related AEs, calculated as event per patient-year, was similar in Child–Pugh class A and class B patients. However, the number of drug-related serious AEs was slightly higher in Child–Pugh class B patients than in class A patients (15% vs 8%).

The aforementioned studies and other small-scale studies summarized in Table 4[43,46,49–52,54–60] have consistently shown that sorafenib can be safely administered to patients with Child–Pugh class B liver function. Most studies have indicated that sorafenib-related AEs do not significantly differ between Child–Pugh class B and class A patients. However, the OS of Child–Pugh class B patients treated with sorafenib remains short (median 3–4 months). The actual survival benefit of sorafenib in Child–Pugh class B patients remains unknown.

Sorafenib for earlier-stage HCC

Because sorafenib suppresses angiogenesis and tumor cell proliferation, the two crucial factors mediating tumor recurrence and progression, it is anticipated that sorafenib may improve the outcomes of HCC following locoregional therapies.

Combining sorafenib and transcatheter arterial chemoembolization (TACE) to treat intermediate-stage (or BCLC stage B) HCC has been investigated in multiple single-arm studies (Table 5).[61–65] In general, the combinations were safe and potentially helpful. The only published Phase III trial, conducted in Japan and Korea, randomized 458 intermediate-stage HCC patients exhibiting ≥25% tumor necrosis or shrinkage after one or two sessions of TACE into the sorafenib or placebo arm. The primary endpoint was TTP by central review. The results revealed that TTP was not significantly improved in the sorafenib arm (median, 5.4 vs 3.7 months).[66] The median time from last TACE to randomization was 9.3 weeks, and the median daily dose of sorafenib was only 386 mg.[66] The relatively long lag in beginning sorafenib treatment after TACE and the low daily sorafenib dose might have contributed to the negative results of the study. The SPACE trial was a placebo-controlled randomized Phase II study that evaluated the efficacy and safety of sorafenib in combination with TACE using doxorubicin-eluting beads for treating intermediate-stage HCC.[67] A total of 307 patients were randomized to receive sorafenib or a placebo continually; all patients received first TACE 3–7 days after the first dose of the studied drugs, and subsequent TACE on defined time points at months 3, 7, and 13, and every 6 months thereafter. The primary endpoint was TTP determined according to independent review. The TTP did not differ significantly between the sorafenib and placebo arms (median, 169 vs 167 days).[67] Several Phase III randomized, placebo-controlled trials evaluating the efficacy of sorafenib in combination with TACE are ongoing.[68,69]

Tumor recurrence develops in more than 70% of HCC patients receiving curative-intent local therapy. Except for possibly effective antiviral agents for carriers of HBV or HCV, there is no currently approved agent exhibiting efficacy in preventing or delaying tumor recurrence in HCC patients who have received curative treatment.[70] The efficacy of sorafenib as an adjuvant therapy for HCC after curative therapy has been explored in the placebo-controlled, randomized Phase III STORM (Sorafenib as adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular CarcinoMa) study. In the trial, 1,100 HCC patients who had underwent curative treatment (surgical resection or local ablation) were randomized to receive either sorafenib 400 mg twice daily or a placebo for 4 years or until disease recurrence. The primary endpoint was recurrence-free survival. However, in a recent press announcement, the study did not meet its primary endpoint.[71]

Table 4 Studies evaluating outcomes of Child–Pugh class A and class B patients treated with sorafenib for advanced HCC

Reference	Child–Pugh class	Patient number	Median treatment duration (months)	Median TTP (months)	Median OS (months)	Key findings about Child–Pugh class B patients treated with sorafenib
Clinical trial						
Abou-Alfa et al,[50,51] 2006	A	98	4.0	5.0	9.5	More likely to have worsening cirrhosis; poorer outcome than Child–Pugh A patients
	B	38	1.8	3.0	3.2	
Pressiani et al,[52] 2013	A	234	4.2	4.2	10.0	Can tolerate and may benefit from sorafenib treatment
	B	63	1.9	3.8	3.8	
Prospective observational study						
Hollebecque et al,[54] 2011	A	100 (54)†	N/A (4.3)	N/A (3.6)	13.0 (10)	Similar and acceptable sorafenib toxicity profile, but poor survival due to liver dysfunction
	B	20 (18)	N/A (2.3)	N/A (2.5)	4.5 (4.5)	
Lencioni et al[46] (GIDEON)* 2014	A	957	3.2#	N/A	N/A	Sorafenib safety profile is similar irrespective of Child–Pugh status
	B	367	2.0#	N/A	N/A	
	C	35	0.9#	N/A	N/A	
Iavarone et al[43] (SOFIA) 2011	A	259	4.2	10	12.7	
	B	37	2.0	6.9	7.7	
Wörns MA et al,[55] 2009	A	15	2.8	N/A	7.2	More likely to have worsening liver dysfunction or failure; should be treated with caution
	B	15	1.8	N/A	3.3	
	C	4	2.9	N/A	3.4	
Retrospective study						
Pinter M et al,[56] 2009	A	26	N/A	2.2	8.3	Higher incidence of severe AE (including GI bleeding)
	B	23	N/A	2.9	4.3	
	C	10	N/A	N/A	1.5	
Ozenne et al,[57] 2010	A	33	5.0	N/A	8.9	Survival was very short. Opportunity of treatment for Child–Pugh B patients is questionable
	B	17	1.8	N/A	2.0	
Wörns MA et al,[58] 2013	A	60	4.0	N/A	10.5	Presence of MVI was a poor prognostic factor; while presence of ascites was not a prognostic factor
	B	42	3.0	N/A	6.0	
	C	8	2.3	N/A	3.0	
Kudo et al,[49] 2012	A	149	N/A	N/A	16.3	Shorter OS for Child–Pugh B patients
	B	39	N/A	N/A	9.3	
Kim HY et al,[59] 2013	A (score =5)	134	N/A	N/A	8.4	Child–Pugh score was important in predicting outcomes; presence of ascites was significant prognostic factor in Child–Pugh B (score 7) patients
	A (score =6)	111	N/A	N/A	5.1	
	B (score =7)	51	N/A	N/A	3.4	
	B (score =8, 9)	29	N/A	N/A	2.6	
Køstner AH et al,[60] 2013	A	43	3.2	N/A	6.6	Child–Pugh B patients had poor OS; routine use of sorafenib for these patients could not be recommended
	B and C	29 and 4	1.5	N/A	3.6	

Notes: *Second interim analysis results; #data were originally reported in months; values reported here were approximates; †data presented in parentheses are those of the case-control study based on 18 Child–Pugh class B patients with 1:3 ratio matched Child–Pugh class A patients.

Abbreviations: AE, adverse event; GI, gastrointestinal; GIDEON, Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; N/A, not available; OS, overall survival; SOFIA, SOraFenib Italian Assessment; TTP, time to progression.

Sorafenib-based combinations: a promising must

In the pivotal SHARP and Sorafenib-AP studies, the objective tumor response rates were only 2% to 3%.[7,8] Combination strategies with the objective of improving the efficacy of sorafenib have been explored extensively (Table 6).

Abou-Alfa et al conducted a randomized Phase II study comparing sorafenib plus doxorubicin versus doxorubicin plus a placebo in patients with advanced HCC.[72] The median TTPs were 6.4 months (95% CI, 4.8–9.2 months) for patients who received doxorubicin plus sorafenib, and 2.8 months (95% CI, 1.6–5 months) for those who received doxorubicin plus the placebo. The median OS was significantly longer in patients receiving the combination (13.7 vs 6.5 months) than in patients who received doxorubicin plus the placebo. However, the combination of sorafenib with doxorubicin resulted in substantially increased toxicities. A Phase III study comparing sorafenib plus doxorubicin with sorafenib alone is ongoing.

To avoid the excessive toxicity related to doxorubicin, several other chemotherapeutic agents have been tested in

Table 5 Clinical studies of sorafenib in combination with TACE for intermediate HCC

Reference	Key eligibility criteria	TACE schedule	TACE method	Patient number	Tumor response (CR + PR + SD)	Median TTP (months)	HR (95% CI) in TTP
Single-arm Phase II study							
Pawlik et al,[61] 2011	Unresectable HCC Child–Pugh A or B7 No prior TACE	1st TACE (1 week after sorafenib) → TACE every 6 weeks	DEB-TACE (Doxo 100 mg)	35	0 + 9% + 86%	N/A	N/A
Park et al,[62] 2012	Unresectable HCC Child–Pugh A or B7 No prior systemic therapy	1st TACE (3 days before sorafenib)* → repeat on demand	Conventional TACE (Doxo 20–60 mg)	50	0 + 44% + 40%	7.1	N/A
Sieghart et al,[63] 2012	Unresectable HCC Child–Pugh A or B No prior TACE Peripheral PVT allowed	1st TACE (2 weeks after sorafenib) → TACE ×2 (every 4 weeks) → optional	Conventional TACE (Doxo 25–75 mg/m^2)	15	10% + 33% + 10%	N/A	N/A
Chung et al,[64] 2013	BCLC-B HCC Child–Pugh A or B7	1st TACE (4–7 days before sorafenib) → TACE on demand (every 6–8 weeks)	Conventional TACE (Doxo 30–60 mg)	147	27% + 24% + 38%	N/A	N/A
Randomized Phase II studies							
Sansonno et al,[65] 2012	BCLC-B HCC Anti-HCV(+) Child–Pugh A No prior targeted therapy	1st TACE (30 days before drug therapy) → TACE (every 4–6 weeks, total number ≦4)	Conventional TACE (Doxo 30 mg + Mito 10 mg)	Sorafenib: 31 vs Placebo: 31	N/A	9.2 4.9	2.5 (1.66–7.56) $P<0.01$
Lencioni et al[67] (SPACE) 2012	Unresectable HCC Child–Pugh A No MVI No prior TACE	1st TACE (3–7 days after drug therapy) → TACE on months 3, 7, 13, and every 6 months thereafter	DEB-TACE (Doxo 150 mg)	Sorafenib: 154 vs Placebo: 153	N/A	5.5[#] 5.4	0.797 (0.588–1.080) $P=0.072$
Randomized Phase III studies							
Kudo et al,[66] 2011	Unresectable HCC (maximum <7 cm) Child–Pugh A No MVI Documented to response to prior TACE	1 or 2 TACE before randomization	Conventional TACE (single of combination of Epi, cisplatin, Doxo, Mito)	Sorafenib: 229 vs Placebo: 229	N/A	5.4 3.7	0.87 (0.70–1.09) $P=0.252$

Notes: *Sorafenib was continued up to 24 weeks; [#]median TTP was reported as 169 days for sorafenib arm and 166 days for placebo arm.

Abbreviations: CI, confidence interval; BCLC, Barcelona-Clinic Liver Cancer; CR, complete response; DEB, drug-eluting bead; Doxo, doxorubicin; Epi, epirubicin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; Mito, mitomycin-C; MVI, macrovascular invasion; N/A, not available; PR, partial response; PVT, portal vein thrombosis; SD, stable disease; TACE, transcatheter arterial chemoembolization; TTP, time to progression.

Table 6 Clinical trials combining sorafenib with chemotherapy or targeted agents for advanced HCC

Reference	Agent(s) to be combined with (target)	Phase	Evaluable patient number	Objective response rate*	Disease control rate*	Median TTP (or PFS) (months)	Median OS (months)
First-line combination with chemotherapy							
Abou-Alfa et al,[72] 2010	Doxorubicin 60 mg/m^2 IV Q3W + sorafenib	II, randomized, double-blind	47	4%	N/A	6.4 (P=0.02)	13.7 (P=0.006)
	Doxorubicin 60 mg/m^2 IV Q3W + placebo		49	2%	N/A	2.8	6.5
Hsu et al,[73] 2010	Tegafur/uracil 125 mg/m^2 (based on tegafur) PO BID	II	53	8%	57%	3.7	7.4
Lee et al,[74] 2012	S-1 50–80 mg/d PO BID d1–14 Q3W (RP2D =80 mg/d)	I	20	5.9%	52.9%	3.9	10.4
Rojas-Hernandez et al,[75] 2013	Capecitabine 850 mg/m^2/d PO d1–7 Q2W	II	14	23%	54%	NR	11.3
Assenat et al,[76] 2013	Gemcitabine 1,000 mg/m^2 IV d1 + Oxaliplatin 100 mg/m^2 IV d2; Q3W	II randomized	47	16%	77%	6.2	13.5
	–		47	9%	70%	4.6	13.0
Yau et al,[77] 2013	Oxaliplatin 85 mg/m^2 IV d1 + Capecitabine 1,700 mg/m^2/d PO d1–14; Q3W	II	51	16%	78%	5.3	11.7
First-line combination with other targeted agents							
Zhu et al,[12] (SEARCH) 2012	Erlotinib 100 mg PO QD (EGFR)	III, randomized, double-blind	362	N/A	43.9%	3.2 (P=0.91)	9.5 (P=0.204)
	Placebo		358	N/A	52.5%	4.0	8.5
Lim et al,[78] 2012	BAY 86-9766 50 mg PO BID (MEK)	II	65	5%	N/A	4	N/A
Choo et al,[79] 2012	Selumetinib (AZD6244) 50–100 mg PO BID (RP2D: 75 mg) (MEK)	I	11	27.3%	N/A	N/A	N/A
Finn et al,[80] 2013	Everolimus 2.5 or 5 mg PO QD (MTD: 2.5 mg) (mTOR)	I	30	0%	N/A	4.5 (2.5 mg qd); 1.8 (5 mg qd)	N/A
Kelley et al,[81] 2013	Temsirolimus 10, 15 mg IV QW (RP2D: 10 mg QW) (mTOR)	I	25	8%	N/A	(5.65; at MTD level)	N/A
Faivre et al,[82] 2011	AVE1642 1,3,6 mg/kg IV QW (IGF-1R)	I	13	0%	N/A	N/A	N/A
Lee et al,[83] 2012	AEG35156 300 mg IV QW (XIAP)	II, randomized, open-label	31	N/A	N/A	(4.0)	N/A
	–		17	N/A	N/A	(2.6)	N/A

Sun et al,[84] 2011	Mapatumumab 3, 10, 30 mg/kg IV Q3W (TRAIL-R1)	I	19	10.5%	N/A	N/A	N/A
Cheng et al,[85] 2012	Tigatuzumab 2, 4, 6 mg/kg IV QW (TRAIL-R2)	I	11	18%	54%	N/A	N/A
Second-line or beyond							
Bitzer et al,[86] 2012	Resminostat (4SC-201) 200, 400, 600, 800 mg PO QD d1–5 Q2W (HDAC)	II, two-arm, parallel, open-label	26	0	N/A	(4.7)	(8.0)
	Resminostat (4SC-201) 600 mg PO QD d1–5 Q2W (HDAC) PO QD d1–5 Q2W (HDAC)		19	0	N/A	(2.2)	(4.1)
O'Neil et al,[87] 2013	Golvatinib (E7050) 200, 300, 400 mg PO QD (c-Met, Kit, RON)	I/II	12 (Phase I)	17% (2 PR)	50%	N/A	N/A

Notes: *The tumor response was defined per RECIST. Objective response rate = CR + PR; disease control rate = CR + PR + SD.

Abbreviations: BID, twice a day; CR, complete response; d, day; EGFR, endothelial growth factor receptor; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; IGF-1R, insulin-like growth factor-1 receptor; IV, intravenous; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; N/A, not available; OS, overall survival; PFS, progression-free survival; PO, per os; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; QD, every day; QW, every week; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended dose for Phase II study; SD, stable disease; SEARCH, Sorafenib and Erlotinib, a rAndomized tRial protoCol for the treatment of patients with Hepatocellular carcinoma; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TTP, time to progression; XIAP, x-linked inhibitor of apoptosis.

combination with sorafenib. Oral fluoropyrimidines are relatively nontoxic and convenient for application. Tegafur/uracil, S-1, and capecitabine in combination with sorafenib have been studied in Phase II and Phase I trials.[73–75] New chemotherapy doublets, such as oxaliplatin plus capecitabine, and gemcitabine plus oxaliplatin, in combination with sorafenib have been reported to yield high tumor response rates and disease control rates in Phase II studies.[76,77]

Sorafenib in combination with other targeted agents holds promise. These combinations may exert greater control over HCC by simultaneously inhibiting multiple survival signaling pathways and thus overcoming resistance to sorafenib. However, most clinical studies on these combinations remain in the early phase (Table 6).[78–87] The combination of sorafenib and MEK inhibitors is a typical example of "vertical blockade"; in other words, the suppression of two signaling molecules of the same pathway.[27] Lim et al reported a Phase II study of BAY 86-9766, an allosteric inhibitor of MEK, in combination with sorafenib as first-line therapy for advanced HCC. The objective response rate was 5% (3/65 evaluable patients).[78] Choo et al reported a Phase I study of AZD6244, another MEK inhibitor, in combination with sorafenib in HCC, yielding an objective response rate of 27% (3/11 evaluable patients).[79] Because the three responders in Lim's study all had RAS-mutant tumors, a study testing this combination in patients with RAS mutation is ongoing.

Simultaneous inhibition of the Raf/ERK/MEK pathway by sorafenib and other signaling pathways by other inhibitors (ie, "parallel blockade") is theoretically sound. Two Phase I studies have examined the combination of mTOR inhibitors, temsirolimus or everolimus, with sorafenib.[80,81] The maximum tolerated doses for the combinations of mTOR inhibitors and sorafenib (everolimus 2.5 mg daily plus sorafenib 400 mg twice daily,[80] and temsirolimus 10 mg weekly plus sorafenib 200 mg twice daily[81]) were unsatisfactory and potentially suboptimal for biological activity. Several preclinical studies have demonstrated that sorafenib can enhance the proapoptosis effect induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in TRAIL-resistant cancer cells, including HCC cells,[17,88–90] thus providing a rationale for combining TRAIL receptor agonists and sorafenib in HCC treatment. Phase I studies of mapatumumab and tigatuzumab, two TRAIL receptor agonists, in combination with sorafenib have been conducted.[84,85] Randomized Phase II studies of these combinations in a first-line setting are ongoing.

In addition, preclinical studies have demonstrated that activation of the EGFR pathway confers resistance to sorafenib in HCC cells, and the combination of EGFR

inhibitors and sorafenib improved the antitumor effect of sorafenib in experimental HCC models.[25,91,92] However, the results of the Phase III randomized placebo-controlled double-blind study testing the combination of sorafenib and erlotinib did not show survival benefit.[12]

Conclusion and future perspectives

Despite numerous clinical and preclinical studies, sorafenib remains the only drug approved for advanced HCC. Recently published clinical trials have indicated that the median OS of the sorafenib arm is now approximately 9 months for Asians and 12 months for non-Asians.[9,11] Preemptive dose modification and the ramp-up strategy of sorafenib prescription have gradually been adopted in daily practice to improve patients' compliance and avoid treatment interruption.

Sorafenib can safely be administered to Child–Pugh class B patients, although the survival advantage remains unclear. Large randomized trials examining the benefits of sorafenib as an adjunctive therapy for intermediate-stage HCC patients receiving locoregional therapies such as TACE, and as an adjuvant therapy for early-stage HCC patients who have undergone curative therapy are ongoing.

Because the clinical benefit of sorafenib is relatively modest, biomarkers predictive of the efficacy of sorafenib must be identified to avoid imposing needless toxicities upon patients who do not benefit from the treatment.[93] Furthermore, in-depth mechanistic studies on sorafenib as well as the proper design and execution of clinical trials are critical for future success. Finally, as our understanding of the landscape of genetic alterations in HCC rapidly improves,[94–99] personalized targeted therapy, with or without sorafenib, will become possible.

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