Biologic and Systemic Therapies for the Treatment of Hepatocellular Carcinoma

24

Richard S. Finn

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, yet systemic treatment options for the disease are limited. Only recently, sorafenib, an oral, small-molecule tyrosine kinase inhibitor of several intracellular proteins suspected to be important in HCC progression, including the platelet-derived growth factor receptor-β (PDGFR), "Raf" kinase, and the vascular endothelial growth factor receptors (VEGFR) including VEGFR 1, 2, and 3, was shown to prolong survival in HCC. While the benefit of sorafenib over placebo is modest (the median survival increased from 7.9 to 10.7 months), it was a significant advance, becoming the first systemic agent to prolong survival in this setting, and has spurred an increase in research at all stages of the disease. Currently, there are an unprecedented number of clinical studies of new agents in HCC. In addition to evaluating these agents in combination with sorafenib, they are being compared directly to sorafenib, after progression on sorafenib, and in combination with locally ablative therapies such as transarterial chemoembolization (TACE) and radio-frequency ablation (RFA) and surgical resection. With this robust activity, we are increasing our understanding of HCC and will likely see significant improvements on the initial observations made with sorafenib. As highlighted here, this will take careful study design, patient selection, and a rational selection of new therapeutic targets.

Introduction

More than any other malignancy, the proper management of patients with hepatocellular carcinoma (HCC) requires a multidisciplinary approach. The disease remains a clinical challenge because it presents as two intimately related medical problems: (1) variable degrees of liver dysfunction and (2) cancer. Liver transplantation remains the

R.S. Finn
Department of Medicine, Geffen School of Medicine at UCLA Ronald Regan Medical Center at UCLA, Los Angeles, CA, USA
e-mail: rfinn@mednet.ucla.edu

D.E. Dupuy et al. (eds.), *Image-Guided Cancer Therapy*, DOI 10.1007/978-1-4419-0751-6_26,

treatment of choice for most patients as it provides a means of correcting both problems. However, most patients are beyond tumor criteria for transplant at presentation, and many that are listed face the reality that they will come off the list while waiting because of tumor progression. Locally ablative therapies such as transarterial chemoembolization (TACE), radio-frequency ablation (RFA), and percutaneous ethanol ablation (PEI) all play a role in managing patients with liver-confined disease but in general are not felt to be curative for most patients. With the above in mind, most patients with HCC will require systemic treatment of their disease at sometime in their disease course. This includes patients that present with advanced disease and also those that have received curative or local therapies and eventually progress. Since the approval of sorafenib, the first systemic agent to improve survival in advanced HCC, interest in HCC as a target for drug development has opened opportunities for the development of new agents in the frontline setting, in second-line setting, and in combination with TACE, RFA, and surgery.

Historical Perspective: Systemic Agents

For many years, HCC has been considered an "orphan disease" in the West. Its incidence has generally been low compared to other tumor types with estimated 16,000 cases of HCC in 2009 versus 219,000, 194,000, 146,000, in lung, breast, and colorectal cancer, respectively, in the United States alone [1]. Nevertheless, many clinical studies have been performed with traditional cytotoxic agents [2]. These studies were often not randomized, but single-arm phase II studies for patients with "unresectable HCC." Even the few studies that were randomized did not show any benefit of newer agents over older ones nor did they demonstrate significant benefit for combinations over single agents.

The reason for the clinical failure of cytotoxics in this disease can be linked to several factors. For one, cytotoxics are associated with significant side effects including bone marrow suppression resulting in infections (from neutropenia) and bleeding (from thrombocytopenia) events, renal insufficiency, and, in some cases, direct hepatotoxicity. In a group of patients with often marginal physiologic reserve, these toxicities are often intolerable. In addition, until recently, studies have assumed that "unresectable" HCC represents one disease entity. Besides the issue of variable outcomes based on liver dysfunction (as measured by either Child-Pugh score or Model for End-Stage Liver Disease (MELD) score), "unresectable" HCC includes patients that have disease that is often associated with variable outcomes based on their tumor burden alone. For example, a patient unresectable because of tumor location will have a different natural history than a patient with portal vein thrombosis and still different from a patient with clear extrahepatic/metastatic spread [3]. Many studies in the past did not stratify for these characteristics and therefore included heterogeneous groups of patients. For this reason, single-arm studies are very difficult to interpret in terms of survival endpoints.

In addition, related to the above two issues is the use of composite endpoints in oncology clinical studies. Endpoints such as progression-free survival (PFS) are commonly used in HCC studies. PFS is typically defined as the time from randomization to either radiographic progression or death from any cause. Given the impact of underlying liver disease on survival, this endpoint may not reflect the true benefit of an anticancer therapy and is clearly affected by patient selection [4].

Other clinical trial factors have to be considered in interpreting clinical trials with systemic agents. One, radiographic evaluation of HCC may require and benefit from newer methods of assessment. While most clinical trials with systemic agents have based clinical activity on response rate, this is not necessarily the most accurate assessment of anticancer activity. Historically bidimensional measurements were used (WHO classification of response) [5] and more recently unidimensional measurements based on the sum of the longest dimensions as defined by RECIST [6]. Several years ago, the European

Association for the Study of the Liver (EASL) put forward newer criteria, taking into account changes in the size of "viable tumor" as measured by enhancement in the arterial phase [7]. This concept again has been put forward as a "modified RECIST" criteria and may have more relevance with the development of novel agents in HCC [8]. Finally, the lack of the use of a consistent staging system has made assessing response across studies challenging. While several staging systems have been proposed, none has been consistently applied to clinical trials. Most recently, the Barcelona Clinic Liver Cancer (BCLC) classification is being adopted in many prospective studies [4].

New Systemic Approaches: Molecular-Targeted Therapeutics

Similar to drug development in other solid-tumor types, new treatment modalities in HCC are focusing on molecularly targeted agents. For years, various cytotoxic agents have been evaluated in HCC based not on any unique biologic characteristics of liver cancer but on the fact that these agents have had activity in other tumor types. However, this empiric approach to drug development has not moved us any further toward improving outcome for patients with liver cancer [2]. Only in the past several years, with the development of sorafenib have we seen for the first time an improvement in overall survival with a systemic agent. This is the result of a well-conducted study with appropriate patient selection, appropriate endpoints, and the use of an agent with biologic rationale for activity in HCC. Table 24.1 compares several agents that are either approved or in advanced-stage clinical evaluation in HCC, and Table 24.2 summarizes selected ongoing clinical trials in HCC.

Table 24.1 Novel systemic agents in development for HCC. *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *FGFR* fibroblast growth factor receptor, *mTOR* mammalian target of rapamycin, *PDGFR* platelet-derived growth factor receptor, *CSF1R* colony-stimulating factor 1 receptor

Agent	Class	Mechanism of action	Target(s)
Bevacizumab	Monoclonal antibody	Blocks VEGF binding toVEGF receptor	VEGF
Brivanib	Small molecule	Tyrosine kinase inhibitor	VEGFR1-3, FGFR1-3
Everolimus	Small molecule	Serine-threonine kinase inhibitor	mTOR
Linifanib	Small molecule	Tyrosine kinase inhibitor	VEGFR-2, PDGFRα-β, FLT3-4, c-kit, CSF1R
Ramucirimab	Monoclonal antibody	Blocks VEGF receptor 2 activation	VEGFR2
Sorafenib	Small molecule	Tyrosine kinase inhibitor	VEGFR2, VEGFR3, PDGFR, FLT-3, c-kit, raf
TSU-68	Small molecule	Tyrosine kinase inhibitor	VEGFR2, FGFR1, PDGFRβ

Sorafenib

Sorafenib is an oral, small-molecule tyrosine kinase inhibitor of several intracellular proteins suspected to be important in tumor progression, including the platelet-derived growth factor receptor-β (PDGFR), "Raf" kinase, and the vascular endothelial growth factor receptors (VEGFR) including VEGFR 1, 2, and 3 [9]. The proposed mechanism of action of sorafenib is shown in Fig. 24.1. This includes potential inhibition of growth-promoting signals within the tumor cell itself as well as inhibition of the tumor vasculature by its ability to block the VEGFR on endothelial cells. Preclinical models have demonstrated the ability of sorafenib to do both, but the actual effects in human tissue have not been assessed [10].

Two large randomized studies have proven a benefit for sorafenib in BCLC stage C liver cancer.

Table 24.2 Selected ongoing clinical trials in HCC

Agent	Clinical development	Study design	Trial ID
Bevacizumab/erlotinib	Phase II	First-line bevacizumab+ erlotinib versus sorafenib	NCT00881751
Brivanib	Phase III	First-line versus sorafenib	NCT00858871
		Second-line after sorafenib, versus placebo	NCT00825955
		Combo with TACE vs TACE + placebo	NCT00908752
Everolimus	Phase III	Second-line after sorafenib, versus placebo	NCT01035229
Linifanib	Phase III	First-line versus sorafenib	NCT01009593
Ramucirimab	Phase III	Second-line after sorafenib, versus placebo	NCT01140347
Sorafenib[a]	Phase III	First-line sorafenib+ erlotinib versus sorafenib	NCT00126620
	Phase III	First-line sorafenib+ doxorubicin versus sorafenib	NCT01015833
	Phase III	Sorafenib or placebo as adjuvant to resection or RFA	NCT0692770
	Phase II	Sorafenib or placebo in combination with TACE	NCT00855218
Lyso-thermo- sensitive doxorubicin	Phase III	Lyso-thermosensitive doxorubicin or placebo in combination with RFA	NCT00617981

[a]currently approved for advanced HCC

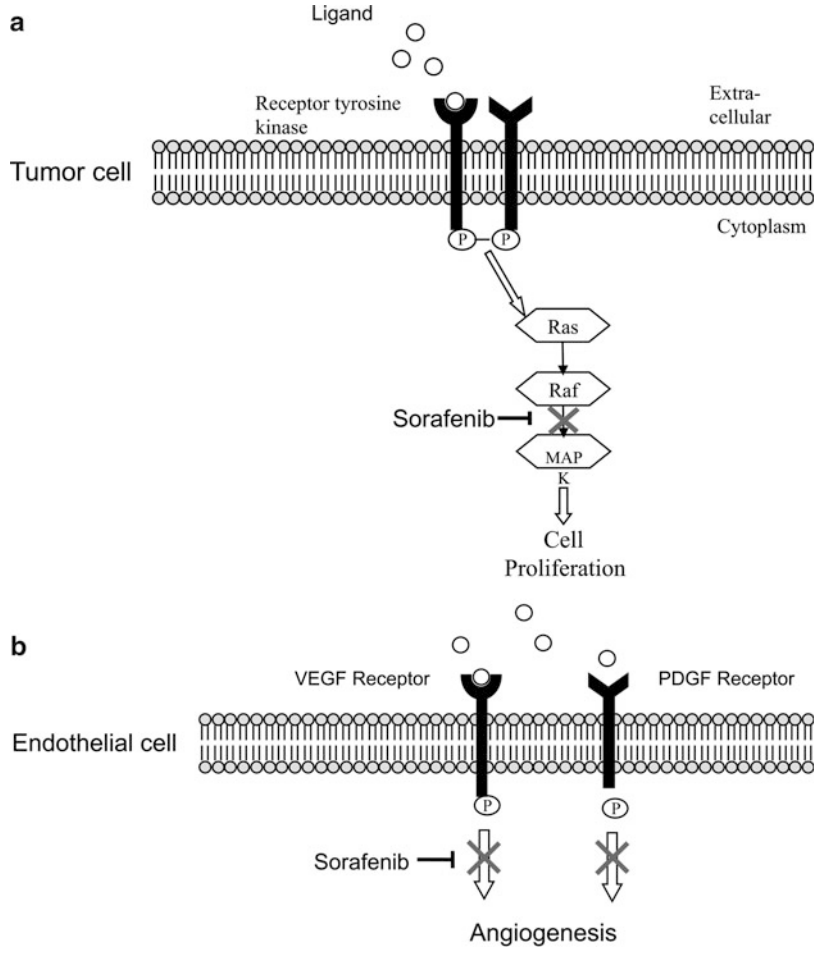

Fig. 24.1 Proposed mechanism of action of the multikinase inhibitor sorafenib. (**a**) Tumor cell, (**b**) endothelial cell (Reproduced with permission from American Association for Cancer Research: Wilhelm SM, et al. Mol cancer ther. October 2008)

Both studies required well-compensated liver disease (Child-Pugh A) at study entry. The Europe-North American study, SHARP, enrolled over 600 patients and randomized them between placebo and sorafenib 400 mg orally twice a day [11]. Patients were stratified for region, performance status, and the presence or absence of macroscopic vascular invasion (portal vein or branches). Patients underwent imaging every 6 weeks to assess radiographic time to tumor progression (TTP). Patients were also assessed for symptomatic endpoints based on a questionnaire. The primary endpoints to the study were overall survival (OS) and the time to symptomatic progression. This study was the first to demonstrate a significant improvement in overall survival with a median OS of 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio (HR) 0.69; 95 % confidence interval, 0.55–0.87; $p < 0.001$). There was no significant difference in the time to symptomatic progression. The median TTP which was 2.8 months in the placebo group increased to 5.5 months in the sorafenib group ($p < 0.001$). Interestingly, this benefit was not driven by an increase in tumor shrinkage on imaging using standard clinical trial criteria, suggesting the benefit was largely driven by inducing stable disease and slowing progression. Common and predictable toxicities in this population included hand-foot skin reaction, anorexia, and diarrhea. Importantly, there was no significant difference in changes in liver dysfunction or bleeding events between the two groups. Seven hundred and sixty five of patients in the sorafenib group received more than 80 % of the planned daily dose.

A second study that evaluated sorafenib in advanced disease was performed in Asia, in a predominantly hepatitis B population [12]. The dosage of sorafenib was the same, and again only patients with Child-Pugh A cirrhosis were selected. Similar to the SHARP study, sorafenib improved OS (6.5 months for patients treated with sorafenib, compared with 4.2 months in the placebo group) (HR 0.68; 95 % CI 5.56–7.56; $p = 0.014$), and the median TTP was 2.8 months in the sorafenib-treated group compared to 1.4 months in the placebo group ($p = 0.0005$). While the magnitude of benefit was the same in both studies as represented by the hazard ratios of 0.69 and 0.68, respectively, both control and treated groups in the Asian study had a lower survival than the corresponding arms in the SHARP study. One explanation for this is the fact that more of the patients in the Asian study had BCLC stage C than in SHARP, which included a population of BCLC stage B patients. Again, the toxicities seen in the Asian study were similar to the SHARP study though there was an increased incidence of any grade hand-foot skin reaction, 45 % in Asia versus 21 % in SHARP. Of note, the wholesale acquisition cost (WAC) in the United States for a 30-day supply of sorafenib 400 mg twice daily is $6,660.95.

A phase II study comparing sorafenib and doxorubicin versus doxorubicin has been completed [13]. This study included 96 patients and randomized them to doxorubicin 60 mg/m^2 every 21 days versus the same dose of doxorubicin with sorafenib 400 mg twice daily. Results showed a median time to progression of 8.6 months in the combination and 4.8 months in the control arm, and the median overall survival was 13.7 months and 6.5 months, respectively. There was a signal for increased cardiac toxicity in the combination arm. There are plans to evaluate this in comparison to sorafenib in the frontline setting in a randomized phase III study (NCT01015833). In addition, there is an ongoing, randomized phase III study comparing the combination of sorafenib and the EGFR small-molecule tyrosine kinase inhibitor erlotinib versus sorafenib alone in patients with advanced HCC (SEARCH study, NCT00126620).

Brivanib

Brivanib is a small-molecule tyrosine kinase inhibitor which is characterized as the first dual-specific kinase with activity against the vascular endothelial growth factor receptors (VEGFR) 1–3 in addition to the fibroblast growth factor receptors (FGFR) 1–3 [14]. A single-agent study evaluated brivanib in the first-line treatment as well as in patients who progressed following one prior anti-angiogenic agent (sorafenib or thalidomide in

a small number of patients). In the first cohort, a largely Asian population of 55 patients with advanced HCC, first-line treatment with brivanib was associated with a median TTP of 2.8 months, a disease control rate of 60 % (47 evaluable patients), and median OS of 10 months [15]. Though not randomized, these data are promising and compare favorably with the results of sorafenib in an Asian-Pacific population [12]. In 46 patients with HCC that was primary refractory to sorafenib (63 %) or refractory to sorafenib after initial benefit (35 %), second-line treatment with brivanib was associated with a disease control rate of 46 % (37 evaluable patients), a median investigator-assessed TTP of 2.7 months, and a median OS of 9.8 months [16]. Brivanib was well tolerated, the most common adverse events being fatigue and diarrhea of generally common toxicity criteria grade 1 or 2. Currently brivanib is in several randomized phase III studies including head-to-head against sorafenib in the frontline setting (NCT00858871) and in the second-line setting versus placebo for patients that progressed on or are intolerant of sorafenib (NCT00825955). These studies build on laboratory data that suggest that FGF signaling is able to mediate resistance to VEGF-targeted therapies [17] and brivanib's ability to block FGFR signaling is one possible mechanism for its activity [18].

Everolimus

Everolimus is an oral small-molecule serine-threonine kinase inhibitor of mTOR (mammalian target of rapamycin) [19]. mTOR is downstream from several receptor tyrosine kinases and is part of the PI3-kinase/AKT signaling cascade. In addition, several studies have suggested that increased mTOR activity is associated with outcome in HCC [20–22]. mTOR is a potent inducer of angiogenesis via its upregulation of the hypoxia-induced gene *HIF1-α*. The mTOR inhibitors rapamycin [23] and everolimus (RAD001) [24] have shown preclinical activity in HCC. Two early-phase single-agent, nonrandomized studies in patients with both treated and untreated HCC defined the toxicity and maximum tolerated dose of everolimus in a well-compensated population. These studies were small and efficacy is difficult to assess. One study compared daily and weekly dosing in 39 patients [25]. The maximum tolerated dose of each was 7.5 and 70 mg, respectively. Common toxicities included stomatitis, rash, diarrhea, and thrombocytopenia. Reactivation of hepatitis B was also observed requiring prophylaxis in future studies. Disease control rates for the daily and weekly cohorts were reported as 71 % and 44 %, respectively. A second study was a phase I/II study evaluating safety and efficacy in 28 patients [26]. This study expanded a cohort at 10 mg daily and reported a median progression-free survival of 3.8 months and median overall survival of 8.4 months. This included a mixed population of sorafenib-naïve and sorafenib-treated patients. These studies have served as a backbone for a newly initiated phase III study of everolimus 7.5 mg daily or placebo in the second-line setting (NCT01035229). In addition, an ongoing study is evaluating the combination of sorafenib and everolimus in the frontline setting (NCT00828594).

Ramucirumab

Ramucirumab is a recombinant human monoclonal antibody that binds to the extracellular domain of the VEGF receptor 2. It was evaluated as a first-line therapy in patients with advanced HCC [27]. The study treated 42 of 43 enrolled patients. The median PFS was 4.0 months (3.9 months for patients with BCLC C and Child-Pugh A and 2.6 months for patients with BCLC C and Child-Pugh B). The median overall survival was 15 months (51 % 1-year survival): 18 months (63 % 1-year survival) for patients with BCLC C and Child-Pugh A and 4 months (0 % 1-year survival) for patients with BCLC C and Child-Pugh B. Three patients (7 %) with extrahepatic disease and BCLC C had partial response, and 18 patients (43 %) had stable disease (50 % disease control rate). The most frequent adverse events were fatigue (67 %), hypertension (41 %), and headache (38 %), and serious adverse events $\geq$ grade 3 in at least 2 patients included ascites (5 % G3),

gastrointestinal (GI) bleeding (5 % G3; 2 % G5), infusion-related reaction (5 % G3), hypoxia (5 % G3), and hypertension (2 % G2, 2 % G3, and 2 % G4). Like everolimus and brivanib, ramucirumab is being evaluated in a phase III study in the second-line treatment for advanced HCC (NCT01140347).

Bevacizumab

Single-agent studies with the monoclonal antibody to VEGF have shown some disease stabilization. One study evaluated two dosages of bevacizumab, 5 and 10 mg/kg administered intravenously once every 2 weeks [28]. Of the 46 patients enrolled, six had objective responses with a response rate of 13 % (95 % CI, 3 %–23 %), and the median survival was 12.4 months (95 % CI, 9.4–19.9 months). In another preliminary study, an early experience uses bevacizumab as a single agent in HCC in a phase II study [29]. Among the 24 patients evaluable for efficacy, 3 (12.5 %) had PR, and 7 (29 %) had SD of at least of 16 weeks.

The combination of bevacizumab and the small-molecule epidermal growth factor receptor (EGFR) inhibitor erlotinib has been studied as well. This combination is based on the scientific hypothesis that there is cross talk between the EGFR and VEGF families. A phase II study of bevacizumab and erlotinib in patients with advanced HCC was studied [30]. Bevacizumab was given at 10 mg/kg intravenously once every 14 days and erlotinib at 150 mg orally daily. Of the 40 patients evaluable for efficacy, 10 patients had PRs with a 25 % response rate. The median PFS was 9 months and OS 15.65 months. This combination is now being evaluated in a randomized phase II study versus sorafenib (NCT00881751).

Linifanib

Linifanib, ABT-869, is a receptor tyrosine kinase inhibitor of VEGFR and PDGFR receptor families [31]. It has been evaluated in a single-arm phase II study in advanced HCC [32]. Data presented reported an interim analysis on 34 of 44 enrolled patients. The majority were Child-Pugh A and 74 % had not received prior treatment. The median TTP was 112 days and median overall survival was 295 days. Some of the most common adverse events were hypertension, fatigue, diarrhea, rash, and proteinuria. A phase III randomized study versus sorafenib is planned (NCT01009593).

Combining Systemic Agents with Other Treatment Modalities

Recognizing that surgical resection and locally ablative techniques are not curative (but life-prolonging), there is obvious interest in improving on these approaches. As in other malignancies, systemic agents added as adjuvants to definitive therapy have been shown to improve survival and, in some case, the cure rate. To date, the lack of active systemic agents has limited the ability to improve on current techniques. However, now that there are active systemic agents, studies are in progress evaluating this hypothesis. While there are numerous smaller phase I and phase II studies, we will highlight the larger studies aimed at registration below.

STORM

The STORM study is a randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment of HCC after curative therapy including surgical resection or RFA (NCT0692770). The study builds on sorafenib's proven efficacy in advanced disease. It aims at enrolling 1,100 patients globally. It aims at treating patients with either sorafenib 400 mg orally twice daily or placebo for a total of 4 years or until recurrence. The primary endpoint will be recurrence-free survival.

SPACE

Like the STORM study, the SPACE study is evaluating a proven systemic therapy, sorafenib, in patients with intermediate-stage HCC (NCT00855218). The study is a phase II study

randomizing patients to either a regimen of TACE with DC beads and doxorubicin versus the same regimen and sorafenib. The study is of scientific interest given the role angiogenesis may play in progression after TACE. The interval, timing, and number of TACE are dictated by the protocol. This study will build on data recently presented that did not demonstrate any benefit of sorafenib added to TACE in an Asian study, though adherence to that protocol seemed poor [33].

BRISK-TA

Brivanib is an oral small-molecule inhibitor of the VEGFR and FGFR that has been studied in a phase II study in advanced untreated and treated HCC. Preliminary activity has initiated a large registration program. Like the SPACE study, the hypothesis is that anti-vascular therapy with TACE can be enhanced with the use of pharmacologic inhibition of angiogenesis with a molecular agent. The BRISK-TA (*B*rivanib Study for Patients at *R*isk-*TA*CE, NCT00908752) study will randomize 870 patients globally with unrespectable HCC to TACE and placebo versus TACE alone. The primary endpoint of the study is overall survival. Unlike the SPACE study that has a regimented TACE schedule, the BRISK study allows for more leeway and is built around TACE "as needed" based on investigator assessment and imaging. Key inclusions are Child-Pugh A or B liver disease and one lesion $\geq$5 cm or multinodular disease with at least one $>$ 3 cm. When completed, it will be the largest TACE study ever completed and will inform us not only about the role of brivanib in this population but also about the natural history of TACE and HCC in this population of patients.

HEAT

Early studies evaluated the sensitizing effects of systemic chemotherapy to thermal ablation to liver tissue [34, 35]. These studies proposed the concept that the area of tissue destruction by radio-frequency ablation (RFA) alone could be achieved by the simultaneous administration of systemic doxorubicin during RFA. This concept is currently being evaluated in a phase III randomized controlled study. The formulation of the study drug in evaluation (*T*hermoDox®) involves the delivery of lyso-thermosensitive doxorubicin in a proprietary liposome that releases drug in the presence of elevated temperatures [36]. The HEAT (*He*patocellular Carcinoma Study of RF*A* and *T*hermoDox, NCT00617981) study is a 600-patient study randomizing patients with larger tumors between RFA and placebo or RFA with simultaneous ThermoDox administration. Key inclusion criteria are Child-Pugh A or B liver disease and no more than four lesions, with at least one $\geq$ 3 cm and none $>$ 7 cm. The primary endpoint of the study is progression-free survival with overall survival as a secondary endpoint. Unfortunately, the sponsoring company Celsion publicly reported on January 31, 2013 that there were no significant differences in progression free survival between the two groups. The overall survival endpoints are unknown at this time.

TSU-68

TSU-68 is an oral small-molecule inhibitor of VEGFR, PDGFR, and FGFR with preliminary single-agent activity in HCC [37]. A phase II study enrolled 101 patients with both Child-Pugh A and B liver disease and randomized them to TACE alone or TACE followed by TSU-68 [38]. The median PFS was 5.2 months with combination versus 4.0 months for TACE alone. The combination seemed well tolerated with the most common serious adverse events being fatigue and liver function abnormalities. A larger study to evaluate its impact on overall survival is required.

Conclusions

The approval of sorafenib has highlighted the unmet medical needs for patient with all stages of HCC. In what was once viewed as a difficult

disease to show benefits in, there are now multiple phase III studies and even more phase I and II studies of newer agents. Currently, the majority of agents in development are antiangiogenic. In principal, the data with sorafenib has validated this class of agent as active in HCC. Now the challenge is improving on sorafenib's impact. To that end, new agents with different chemical properties and targets are being evaluated. These include agents with activity against the FGF and mTOR pathways. While direct comparisons to sorafenib are required in the frontline setting, in the population of patients that progress on sorafenib, there is no proven agent and placebo-controlled trials are required. In addition, new combinations of targeted agents hold promise for exploiting several oncogenic pathways simultaneously. It is possible that the greatest gains in survival will come from the use of these agents in earlier stage of disease. These studies are ongoing as newer agents show promising activity; they will be introduced in these settings as well.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225–49.
2. Thomas MB, Zhu AX. Hepatocellular carcinoma: the need for progress. J Clin Oncol. 2005;23:2892–9.
3. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
4. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:698–711.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47:207–14.
6. James K, Eisenhauer E, Christian M, Terenziani M, Vena D, Muldal A, Therasse P. Measuring response in solid tumors: unidimensional versus bidimensional measurement. J Natl Cancer Inst. 1999;91:523–8.
7. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
8. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
9. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008;7:3129–40.
10. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64:7099–109.
11. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378–90.
12. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34.
13. Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA 2010;304(19):2154–60.
14. Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, Zheng X, et al. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f] [1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). J Med Chem. 2008;51:1976–80.
15. Raoul JL, Finn RS, Kang YK, et al. An open-label phase II study of first- and second-line treatment with brivanib in patients with hepatocellular carcinoma (HCC). J Clin Oncol. 2009;27:4577.
16. Finn RS, Kang YK,Mulcahy M, Polite BN, Lim HY, Walters I, Baudelet C, et al. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2012;18(7):2090–8.
17. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer Cell. 2005;8:299–309.
18. Huynh H, Ngo VC, Fargnoli J, Ayers M, Soo KC, Koong HN, Thng CH, et al. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. Clin Cancer Res. 2008;14:6146–53.
19. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008;27:5497–510.

20. Sahin F, Kannangai R, Adegbola O, Wang J, Su G, Torbenson M. mTOR and P70 S6 kinase expression in primary liver neoplasms. Clin Cancer Res. 2004;10:8421–5.
21. Sieghart W, Fuereder T, Schmid K, Cejka D, Werzowa J, Wrba F, Wang X, et al. Mammalian target of rapamycin pathway activity in hepatocellular carcinomas of patients undergoing liver transplantation. Transplantation. 2007;83:425–32.
22. Villanueva A, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, et al. Pivotal role of mTOR signaling in hepatocellular carcinoma. Gastroenterology. 2008;135:1972–83, 1983 e1971–11.
23. Wang Z, Zhou J, Fan J, Qiu SJ, Yu Y, Huang XW, Tang ZY. Effect of rapamycin alone and in combination with sorafenib in an orthotopic model of human hepatocellular carcinoma. Clin Cancer Res. 2008; 14:5124–30.
24. Huynh H, Chow KH, Soo KC, Toh HC, Choo SP, Foo KF, Poon D, et al. RAD001 (everolimus) inhibits tumour growth in xenograft models of human hepatocellular carcinoma. J Cell Mol Med. 2009; 13:1371–80.
25. Chen L, Shiah HS, Chen CY, et al. Randomized, phase I, and pharmacokinetic (PK) study of RAD001, and mTOR inhibitor, in patients (pts) with advanced hepatocellular carcinoma (HCC). J Clin Oncol. 2009;27:4587.
26. Blaszkowsky LS, Abrams TA, Miksad RA, et al. Phase I/II study of everolimus in patients with advanced hepatocellular carcinoma (HCC). J Clin Oncol. 2010;28:e14542.
27. Zhu AX, Finn RS, Mulcahy MF, et al. A phase II study of ramucirumab as first-line monotherapy in patients (pts) with advanced hepatocellular carcinoma (HCC). J Clin Oncol. 2010;28:4083.
28. Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, Chen H, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol. 2008;26:2992–8.
29. Malka D, Dromain C, Farace F, Horn S, Pignon J, Ducreux M, Boige V. Bevacizumab in patients (pts) with advanced hepatocellular carcinoma (HCC): preliminary results of a phase II study with circulating endothelial cell (CEC) monitoring. J Clin Oncol. 2007;25:4570.
30. Thomas MB, Morris JS, Chadha R, Iwasaki M, Kaur H, Lin E, Kaseb A, et al. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol. 2009;27(6):843–50.
31. Albert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, et al. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. Mol Cancer Ther. 2006;5:995–1006.
32. Toh H, Chen P, Carr BI, et al. A phase II study of ABT-869 in hepatocellular carcinoma (HCC): interim analysis. J Clin Oncol. 2009;27:4581.
33. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresctable hepatocellular carcinoma. Eur J Cancer. 2011;47(14): 2117–27.
34. Ahmed M, Monsky WE, Girnun G, Lukyanov A, D'Ippolito G, Kruskal JB, Stuart KE, et al. Radiofrequency thermal ablation sharply increases intratumoral liposomal doxorubicin accumulation and tumor coagulation. Cancer Res. 2003;63:6327–33.
35. Goldberg SN, Kamel IR, Kruskal JB, Reynolds K, Monsky WL, Stuart KE, Ahmed M, et al. Radiofrequency ablation of hepatic tumors: increased tumor destruction with adjuvant liposomal doxorubicin therapy. AJR Am J Roentgenol. 2002;179:93–101.
36. Poon RT, Borys N. Lyso-thermosensitive liposomal doxorubicin: a novel approach to enhance efficacy of thermal ablation of liver cancer. Expert Opin Pharmacother. 2009;10:333–43.
37. Kanai F, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, Kondo Y, et al. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2011;67:315–24.
38. Arai Y, Inaba T, Yamamoto T, et al. A randomized Phase II study of TSU-68 in patients (Pts) with hepatocellular carcinoma (HCC) treated by transarterial chemoembolization (TACE). J Clin Oncol. 2010; 28:4030.