Beyond chemotherapy: systemic treatment options for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a major worldwide problem. Multiple chemotherapeutic agents have been used both as single agents and in combination to treat advanced HCC, but until recently none have been shown to improve overall survival. Sorafenib is a multitargeted tyrosine kinase inhibitor (TKI) that was the first systemic therapy to demonstrate improved overall survival among patients with advanced HCC in a phase III trial. Although sorafenib shifted the focus of HCC therapeutics to targeted agents, it produced differential outcomes among HCC patients according to etiology [i.e., hepatitis C virus (HCV) versus hepatitis B virus (HBV)] reflecting the difficulty of treating a heterogenous malignancy like HCC. A large number of additional targeted agents have subsequently been evaluated in HCC, such as sunitinib, regorafenib, and brivanib, and have proven inferior to sorafenib. However, several new agents that target c-MET and VEGF have shown promise in the phase II setting and are now being evaluated in randomized trials. This review will review the failures and recent successes reported in the HCC literature with a focus on targeted agents.

Keywords: Hepatocellular carcinoma (HCC); systemic therapy; tyrosine kinase inhibitor (TKI); chemotherapy; unresectable; targeted therapy

Introduction

Hepatocellular carcinoma (HCC) is a major worldwide health problem. It is the fifth leading diagnosis of cancer, and the second most frequent cause of cancer death in the world, accounting for estimated 782,000 new liver cancer cases and 746,000 cancer deaths (1). While hepatitis B and C are the main worldwide culprits of HCC, alcohol related cirrhosis and NASH cirrhosis are thought to be the major contributors in the United States (2). HCC treatment depends on the size and location of the tumors. If discovered early, curative approaches include resection and liver transplantation. Local ablative procedures such as transarterial chemoembolization and radiofrequency ablation can convert ineligible patients into transplant candidates. Unfortunately, most patients present with advanced disease. In the setting where patients are not candidates for curative therapy or have failed local control approaches, systemic therapy is the next option. In this review, we will briefly review historical systemic options and then focus on sorafenib and the new targeted agents.

Chemotherapy

Single agent chemotherapy

HCC is a chemoresistant tumor. Multidrug resistance protein expression, such as P-glycoprotein and p53, and drug efflux mechanisms render chemotherapeutic agents only minimally effective (3,4). In 1975, Olweny *et al*. published one of the first studies using single agent doxorubicin in 14 patients with histologically proven HCC (5). The results were promising, with 3 of 11 evaluable patients showing a complete response and an overall 79% response rate. However, subsequent trials failed to show meaningful benefit and also documented significant toxicities from

Table 1 Single agent chemotherapy				
Study	Agent	No. of patients	Response rate (%)	OS
Olweny *et al*. (5)	Doxorubicin	14	79.0	8 months
Lai *et al*. (6)	Doxorubicin	106	8.3	10.6 weeks
Tan *et al*. (8)	Epirubicin	13	23.0	11 weeks
Pohl *et al*. (9)	Epirubicin	52	9.1	16.2 months (in responders)
Yang *et al*. (14)	Gemcitabine	28	17.8	18.7 weeks
O'Reilly *et al*. (15)	Irinotecan	14	7.0	8.2 months
Patt *et al*. (16)	Capecitabine	37	11.0	10.1 months
Lai *et al*. (10)	Mitoxantrone	20	0	13 weeks

treatment. Even among studies supporting chemotherapy activity, the benefit was of short duration (6,7). Epirubicin and mitoxantrone are other anthracyclines that have been studied, with response rates ranging from 10% to 25% (8-10). Single agent capecitabine, gemcitabine, irinotecan, and others have been used, but the responses were minimal and none provided a survival advantage (10-13) (see *Table 1*).

Combination therapy

Combination chemotherapy regimens have been used with some success. The most well published regimen consists of cisplatin, interferon alpha, doxorubicin, and infusional 5-FU, otherwise known as the PIAF regimen. A phase III randomized, open-label trial included 188 previously untreated patients with histologically confirmed unresectable or metastatic HCC who were randomized to doxorubicin versus PIAF (17). Overall response rate in the doxorubicin group was 10.5% as opposed to 20.9% in the PIAF group (P=0.058). The overall survival in the PIAF group was approximately two months longer (8.67 *vs.* 6.83 months), but this also was not statistically significant (P=0.83). The toxicity of this regimen is important to note. PIAF produced much more neutropenia (82% *vs.* 63%, P=0.003), thrombocytopenia (57% *vs.* 24%, P<0.001), and hypokalemia (7% *vs.* 0%, P=0.007). Generally, this regimen is not recommended unless the patient has an excellent performance status and can tolerate a rigorous combination regimen.

Combination capecitabine and oxaliplatin (CapeOX) was studied in a single arm phase II trial of 50 previously untreated patients with histologically proven HCC who were not suitable for surgical resection, liver transplantation, or local ablation techniques. As with other agents, the objective response rate was low at 7%, but the

disease control rate was 72% with a median duration of 5.4 months (range, 2.2 to 20.5 months). Median overall survival was 9.3 months (18).

Oxaliplatin has also been combined with 5-FU and leucovorin (FOLFOX) in an open label phase III trial randomizing 371 previously untreated advanced HCC patients to FOLFOX versus doxorubicin (19). Initially presented at ASCO 2010, FOLFOX was associated with an increased progression free survival (3 *vs.* 1.8 months, P<0.01) and median overall survival (6.5 *vs.* 4.9 months, P=0.07) compared to patients treated with single agent doxorubicin. A 7-month ad-hoc followup analysis showed persistent overall survival trend, however, the study did not achieve its primary overall survival endpoint. Median overall survival for FOLFOX was much lower than reported for sorafenib (Nexavar®, Bayer Pharmaceuticals) in the pivotal SHARP trial (see "sorafenib" section). The authors noted that this trial was designed before definitive sorafenib data was published. Cross study comparison is inherently flawed, but it is important to recognize that SHARP only included 20% of patients with hepatitis B virus (HBV) while this trial had more than 90% of patients with HBV. It is interesting to consider that in the Asian sorafenib trial (see "sorafenib" section), with approximately 70% hepatitis B positive patients, the median OS was exactly the same as this FOLFOX study. Conceivably, this combination is a viable option for patients who may not have ready access to sorafenib.

Finally, combination oxaliplatin and gemcitabine (GEMOX) was studied in advanced HCC with an overall response rate of 19% with 58% having disease stabilization in a phase II trial of 21 HCC patients (20). Other combination cytotoxic regimens include cisplatin and doxorubicin, cisplatin and capecitabine, gemcitabine and cisplatin, and gemcitabine and pegylated liposomal

Table 2 Combination chemotherapy

Study	Regimen	No. of patients	PFS/TTP	Response rate (%)	OS
Yeo *et al*. (17)	PIAF	188	N/A	20.9	8.67 months
Taïeb *et al*. (20)	GEMOX	21	5 months	19.0	12 months
Louafi *et al*. (25)	GEMOX	32	6.3 months	18.0	11.5 months
Lee *et al*. (21)	Cisplatin/Dox	42	6.6 months (TTP)	18.9	7.3 months
Qin *et al*. (19)	FOLFOX	371	3 months	8.2	6.5 months
Lombardi *et al*. (24)	Gem/Doxil	41	5.8 months (TTP)	24.0	22.5 months
Parikh *et al*. (23)	Gem/Cisplatin	30	18 wks (TTP)	20.0	21 weeks
Boige *et al*. (18)	CapeOx	50	4.1 months	7.0	9.3 months

doxorubicin, although it is not clear if any of these regimens confers a survival benefit (21-24) (See *Table 2*).

Targeted therapy

Hepatocarcinogenesis is a complex system of pathways and alterations that has yet to be completely elucidated. What is known about these pathways is that they include growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin like growth factor (IGF). Although these growth factors activate multiple downstream pathways, the RAS/MAPK pathway is important for each one. Activation of RAS/MAPK may lead to HCC growth and proliferation. EGF binds to its cognate receptor, the extracellular domain of epidermal growth factor receptor (EGFR), triggering signal transduction through the RAS/MAPK pathway. VEGF binds to its cognate receptor, VEGFR, promoting HCC angiogenesis. HGF binds to the c-MET receptor, also upstream of the RAS/MAPK pathway. In one particular study, forty percent of patients with HCC were found to express MET and MET inhibition is a promising therapeutic target (26-30). Discussion of all potential pathways is beyond the scope of this review, but we will discuss relevant literature for these important HCC targets.

Anti-VEGF agents

Sorafenib

Elevated expressions of VEGF ligand and receptor have been found in plasma and liver biopsy samples of patients with HCC (31,32). In addition, elevated levels of serum VEGF levels are associated with a worse prognosis (33).

For these reasons, targeted VEGF therapies have been a key area of drug development. Sorafenib (Nexavar®, Bayer Pharmaceuticals) changed practice as the first HCC therapy to show a statistically significant and clinically meaningful overall survival benefit. Sorafenib inhibits multiple tyrosine kinases, including VEGFR 1, 2, and 3, targeting angiogenesis pathways. In a phase II trial, 137 patients with advanced HCC treated with sorafenib had a median overall survival of 9.2 months (34). Based on this, Llovet *et al*. proceeded with the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, a phase III study that randomized 602 patients with advanced HCC with preserved liver function and no prior systemic treatment to sorafenib versus placebo (35). Patients in the sorafenib arm had a median overall survival of 10.7 *vs*. 7.9 months in the placebo arm (P<0.001). Although only seven patients (2%) in the sorafenib group experienced a partial response, 204 patients (67%) had disease stability. Patients were primarily from Western countries with Child Pugh A cirrhosis. Approximately 30% of patients had hepatitis C virus (HCV) infection, 20% had HBV infection, and 25% had alcoholic liver disease. While this does not reflect the demographics of HCC worldwide, this is the first agent to consistently show a survival benefit in 30 years of trials. Approved by the Food and Drug Administration in November 2007, sorafenib is now the standard of care for first line systemic treatment in advanced HCC.

To confirm the results of the SHARP trial in a different patient population, sorafenib was studied in a predominantly Asian population. In a phase III trial with inclusion criteria that mirrored the SHARP trial, 229 patients with Child Pugh A cirrhosis were randomized to sorafenib versus placebo (36). The median overall survival in the sorafenib cohort was 6.5 *vs*. 4.2 months in the placebo arm [hazard

ratio (HR) 0.68; 95% CI, 0.50-0.93; P=0.014]. While a statistical significant survival benefit was achieved, the numerical benefit was less than that reported in the SHARP trial despite identical entry criteria and risk stratification. Possible explanations for this include a study population with poorer performance status, more prior therapies, more severe liver disease despite Child Pugh A cirrhosis status, or different disease characteristics (more patients with Hepatitis B) compared to the SHARP trial population.

In both the SHARP trial and the trial by Cheng *et al.* (36), the entry criteria were limited to patients with Child Pugh A cirrhosis (only about 5% of both trials had Child Pugh B cirrhosis). This excluded a large portion of patients who concominantly have HCC and more advanced liver disease. Presented at ASCO 2013, the results from the Global Investigation of therapeutic Decisions in HCC and of its treatment with sorafeNib (GIDEON) trial (37), suggested that sorafenib can be safely used in patients with Child Pugh Class B cirrhosis. GIDEON was a non-interventional, surveillance trial that observed over 3,000 patients treated with sorafenib and followed for response and adverse events. Interestingly, the rate of drug related adverse events were comparable between Child Pugh A and Child Pugh B liver disease. However, those with more advanced disease as indicated by a worse Child Pugh score had a lower median overall survival.

Sorafenib has been studied in combination with other known active agents. In a randomized phase II trial, patients with inoperable HCC without prior systemic treatment were administered doxorubicin with or without sorafenib (38). Combination doxorubicin and sorafenib improved median time to progression (6.4 *vs.* 2.8 months, P=0.02) and median overall survival (13.7 *vs.* 6.4 months; P=0.006) compared to single agent doxorubicin. With the positive results of SHARP, an interim analysis of this trial was conducted, prompting its premature closure due to lack of benefit in the single agent arm. A phase III trial is currently ongoing with combination doxorubicin and sorafenib more appropriately being compared to single agent sorafenib (39).

Sunitinib

With the success of sorafenib, the focus of HCC drug development has now shifted to other molecularly targeted agents. Sunitinib (Sutent®, Pfizer) is a multi-targeted tyrosine kinase inhibitor (TKI) to VEGF 1, 2, and 3. Sunitinib's antiangiogenic properties suggested activity in HCC and it was evaluated in a single arm phase II study

with 37 previously untreated patients with only a partial response in one patient. Its primary endpoint of objective responsive was not met, but there was a stable disease rate of 35% (40). A phase III study that randomized over 1,000 patients to sunitinib versus sorafenib was stopped early due to concerns for futility and safety. At followup, the study actually showed a statistical improvement in median overall survival favoring sorafenib over sunitinib (10 *vs.* 8.1 months, P=0.0019). Sunitinib was noted to cause more grade 3 and 4 adverse events, occurring in 82% and 73% of patients, respectively (41). Another phase II study was recently reported confirming these phase III results. In 24 patients with advanced HCC without prior systemic therapy, there was a significant worsening of liver functional reserve after sunitinib. Despite a partial response in four patients (12%), grade 3 and 4 adverse events occurred in 80% of patients (42).

Bevacizumab

Bevacizumab (Avastin®, Genentech/Roche), a recombinant humanized monoclonal antibody targeting soluble VEGF-A, was evaluated in 46 HCC patients with Child Pugh A or B cirrhosis and one or less prior systemic therapy who received single agent bevacizumab using doses of 5 and 10 mg/kg every 2 weeks. Of these patients, six had an objective response (13%), including one complete response and five partial responses (43). The median PFS was 6.9 months, median overall survival was 12.4 months, and 53% of the patients were alive at one year. Circulating VEGF levels were decreased from baseline in all patients in the study. With this data, GEMOX and bevacizumab were combined in a phase II trial of 33 patients with unresectable or metastatic HCC who had two or fewer systemic therapies and CLIP score less than three. No patients had a complete response, but six patients had a partial response (20%) and eight patients had stable disease (27%). Median PFS was 5.3 months and overall survival was 9.6 months (44).

Thalidomide

Thalidomide's (Thalomid®; Celgene Corporation, Warren, NJ) antiangiogenic properties were also explored in HCC, but with disappointing results. In a phase II study of 27 previously treated and untreated patients, one patient had normalization of alpha fetal protein (AFP) and a partial response noted on imaging while two other patients experienced stable disease (45). Another phase II trial enrolled 37 patients, including 13 who had progression

after prior therapy, and had similar results with about a 30% stable disease rate while one patient had a partial response (3%) and one patient had a minor response (3%) (46). A phase III trial was opened in 2005, but terminated in 2011 due to lack of patient accrual (47).

EGFR blockade

Erlotinib

Epidermal growth factor receptor (EGFR1) overexpression has been identified in HCC, suggesting that EGFR activation is a potential pathway to HCC development (48). Erlotinib (Tarceva®, Genentech/OSI Pharmaceuticals) is an oral selective TKI of EGFR1, approved for use in non-small-cell lung cancer and advanced pancreatic adenocarcinoma. In a multi-institutional phase II study, erlotinib was administered to 38 patients with surgically unresectable or metastatic HCC, one or fewer prior systemic therapies, and mainly Child Pugh A cirrhosis. Of 34 evaluable patients, 3 (9%) experienced a partial response and 17 (50%) had disease stability. The median overall survival was 13 months, which is superior to historic controls. Grade 3 and 4 adverse events, however, were greater than 60%. Although one of the intended aims of the trial was to stratify response according to the EGFR status, the samples were incomplete and EGFR status was not known in many of these patients (49). Another phase II trial combined erlotinib with bevacizumab for dual EGFR and VEGF blockade. Forty patients with unresectable advanced HCC who had one or fewer prior systemic therapy at a single institution were enrolled, most of whom had Child-Pugh A cirrhosis (85%). Of these patients, 10 (25%) had a partial response and 17 (43%) had stable disease or minor response. The median PFS was nine months and the median overall survival was 15.7 months. For unclear reasons, and in contradiction to the single agent erolotinib data, very few grade 3 or 4 toxicities occurred (50). Combination erlotinib plus bevacizumab has not been compared to sorafenib.

Cetuximab

Cetuximab (Erbitux®, Bristol Meyers Squibb) is a chimeric monoclonal antibody targeting EGFR1 that blocks EGFR dimerization and phosphorylation. It is approved for use in patients with advanced colorectal carcinoma and head and neck tumors. A phase II study examined cetuximab in advanced HCC among 30 patients who had up to two prior

systemic therapies (51). No patients achieved an objective response, but five patients (17%) had stable disease with a median duration of 4.2 months. Median PFS was 1.4 months and median overall survival was 9.6 months. EGFR protein expression by immunohistochemistry (IHC) could not be correlated to clinical benefit from cetuximab.

Cetuximab was further investigated in combination with CapOX (52) in 29 patients with Child-Pugh A or B cirrhosis with advanced HCC and no prior systemic therapy. Of 24 evaluable patients, 3 (12.5%) had partial response while 17 (71%) had stable disease, for a disease control rate of 83%. The median progression free survival was 3.3 months, and the median overall survival was 4.4 months, which was quite a bit shorter than using either single agent cetuximab or FOLFOX alone. The reasons for the short TTP, PFS, and OS were not clear.

Lapatinib

Since EFGR1 heterodimerizes with HER2 (EGFR2), dual blockade of these targets was postulated to have efficacy in treating HCC. Lapatinib (Tykerb®, GSK) is an oral irreversible dual inhibitor of EGFR and HER2, currently approved for use in metastatic breast cancer. In a phase II trial, this drug was evaluated in 27 patients with unresectable HCC who had one or less prior systemic therapies (19% had 1 prior therapy). As with many of other EGFR inhibitor trials, lapatinib did not produce any objective responses. However, 10 (40%) patients had stable disease that lasted for over three months in six patients and over one year in two patients. The median PFS was 1.9 months and the median overall survival was 12.6 months. HER2/neu was not overexpressed per fluorescence in situ hybridization (FISH), consistent with other reports that HER2 overexpression in HCC is varied (53).

c-MET blockade and other targeted agents

Tivantinib

Tivantinib is a TKI of c-MET, which can be overexpressed or mutated in many tumor cell types and plays a key role in cell proliferation, survival and metastasis. The c-MET protein is a receptor tyrosine kinase also known as HGF. Overexpression of c-MET portends a worse prognosis in patients with HCC. A randomized phase II trial evaluated 107 previously treated patients and showed a benefit for patients with HCC and a high c-MET expression

treated with tivantinib versus placebo in the second line setting. Patients in the treatment arm with high c-MET expression had a significantly increased time to progression (2.9 *vs.* 1.5 months), progression free survival (2.4 *vs.* 1.5 months, P=0.01) and disease control rate (50% *vs.* 20%) (54). Despite a crossover design, a survival benefit trend favored tivantinib. Based on this data, a phase III trial (55) is currently underway, assigning 303 patients to receive tivantinib versus placebo in the second line setting (NCT01755767).

Cabozantinib

Cabozantinib is another promising c-MET inhibitor. It is an oral inhibitor of c-MET and VEGFR2, currently being studied in multiple solid tumors. At ASCO 2012, a phase II trial was presented using cabozantinib in 41 patients with advanced HCC who had no more than one prior systemic treatment. Three patients had a partial response, but 28 patients (78%) had evidence of tumor regression on imaging. As of September 2013, a phase III trial has been opened to further explore the role of this drug in treating HCC (56).

Axitinib

Axitinib (Inlyta®, Pfizer) is a multi-TKI targeting VEGFR 1, 2, 3, PDGFR, and c-Kit. At ASCO GI 2012, interim data from an open-label phase II trial was presented using axitinib in the second-line setting. Data on 15 of the 29 enrolled patients who progressed on prior TKI or anti-VEGF therapy were presented. Of nine patients evaluable for response, there was one partial response with three other patients having tumor shrinkage. Side effects included hypertension, diarrhea, hand foot syndrome, and fatigue. Adverse events required dose reductions in 60% of patients. The full report on this study is pending (57).

Regorafenib

Regorafenib (Stivarga®, Bayer) is a promiscuous multikinase inhibitor with targets including VEGFR2 and 3, Ret, Kit, PDGFR and Raf kinases, approved for metastatic colorectal cancer and metastatic gastrointestinal stromal tumors (GIST). In an open-label phase II trial enrolling 36 patients who progressed on first line sorafenib, the disease control rate was 72% (26 patients), median time to progression was 4.3 months, and median overall survival was 13.8 months.

The main toxicities were hand foot syndrome, fatigue, diarrhea, hypothyroidism, and hypertension, with rare grade 3 or 4 adverse events (58). A phase III trial using regorafenib versus placebo in patients who have progressed on sorafenib is ongoing (59).

Linifanib

Linifanib, a TKI of VEGF and PDGFR was studied in a phase II trial involving 44 predominantly Asian patients had up to one prior therapy and demonstrated an objective response rate that was greater than 10% with only mild toxicities (11). In an open-label phase III study, over 1,000 patients were randomized to linifanib versus sorafenib in the first line setting. Patients had advanced HCC, Child Pugh A cirrhosis, and were predominantly Asian. The primary endpoint was overall survival, evaluating both noninferiority and superiority. The median overall survival was 9.1 months compared to 9.8 months on sorafenib, although linifanib had a longer TTP of 5.4 *vs.* 4.0 months (P=0.001). The overall response rate was 13% in the linifanib arm, however more patients in this arm had dose interruptions and reductions. Thus far, this study has not met its endpoint goals (12).

Brivanib

VEGF and fibroblast growth factor receptor signaling are both implicated in HCC. Brivanib is a selective dual receptor inhibitor of both (13). In a phase III trial of patients who progressed after sorafenib, 395 patients with advanced HCC were randomly assigned in a 2:1 fashion to receive brivanib versus placebo. All patients had previously received sorafenib and the primary endpoint was overall survival. Time to progression (4.2 *vs.* 2.7 months, P<0.001) and overall response rate (10% *vs.* 2%, P=0.003) both favored brivanib. However, no difference was found for overall survival (9.4 *vs.* 8.2 months, P=0.3307), missing the study's primary endpoint (60).

Brivanib was also studied in the first line setting in a phase III noninferiority trial comparing it to sorafenib among 1,155 patients with advanced HCC who were not eligible for surgical and/or locoregional therapies. The primary endpoint was overall survival, which the study did not meet. Overall median survival was 9.5 months in the brivanib arm versus 9.9 months in the sorafenib arm (HR 1.07, P=0.312). Patients receiving brivanib had a marginally higher objective response rate of 12 % *vs.* 9% compared

Table 3 Promising targeted agents

Study	Agent	No. of pts	PFS/TTP (months)	OS (months)	Response rate, %	Phase
Bekaii-Saab *et al*. (53)	Lapatinib	27	1.9	12.6	0	II
McNamara *et al*. (57)	Axitinib	15	N/A	N/A	33 (3/9)	II
Rimassa *et al*. (54)	Tivantinib	107	2.4	6.6	1 (1/107)	II
Bruix *et al*. (58)	Regorafenib	36	4.3	13.8	3 (1/36)	II
Verslype *et al*. (56)	Carbozantinib	41	4.2	N/A	8	II
Cainap *et al*. (12)	Linifanib	1,035	5.4	9.1	13	III
Llovet *et al*. (60)	Brivanib	395	4.2 (TTP)	9.4	10	III
Johnson *et al*. (61)	Brivanib	1,155	4.2 (TTP)	9.5	12	III

to the sorafenib arm. Adverse events of any grade were higher in the sorafenib arm, while there were more grade 3 hyponatremia, hypertension, and fatigue in patients receiving brivanib. Unfortunately, brivanib appeared to be less well tolerated than sorafenib with treatment discontinuation due to side effects in 43% of the patients compared to 33% of patients on sorafenib (61). (See *Table 3* for targeted agents).

Discussion

HCC drug development has been marked by a series of disappointing study results. Initial signals of doxorubicin activity over 30 years ago were shattered by the reality of subsequent poor trial outcomes. Since then, therapeutic focus has shifted to targeted therapies that block transduction through the RAS/MAPK pathway known to drive tumorigenesis, including for HCC. Sorafenib, a multi-targeted kinase inhibitor, was the first agent that has consistently demonstrated an overall survival advantage over placebo and other investigational agents, and remains the front-line standard of care for advanced HCC. A variety of reasons can be offered to explain the intransigent nature of HCC. HCC is notorious for tumor heterogeneity introducing the likelihood of resistance. Pathways leading to HCC are also varied, including viral hepatitis, alcohol, and inflammation. In fact, even among patients with viral hepatitis, sorafenib appears to confer a more salutary effect on those without HBV. As has been true with many other historically resistant tumors, enhanced understanding of HCC tumorigenesis pathways holds the promise for finally altering the natural history of this terrible disease. Targeted agents against angiogenesis, and EGFR and c-MET signaling are encouraging first steps. Future research will

focus on continued understanding of HCC drivers and combination therapies.

Footnote

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