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REVIEW

Treatment of Advanced Hepatocellular Carcinoma: Sorafenib and Beyond

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Abstract: Better understanding of the molecular events involved in hepatic carcinogenesis has led to a new era of targeted therapy for the treatment of advanced HCC. Sorafenib is the first and only systemic agent that has been approved to show the survival benefit in advanced HCC. In addition, results from phase I and II studies of other molecularly targeted agents are promising, however larger phase III studies are needed to determine what role these agents will play. This review will explore the data surrounding the efficacy of sorafenib in various clinical settings, dose modification and the management of toxicities, and the promise of new therapeutic agents.

Keywords: Hepatocellular Carcinoma, sorafenib, molecular targeted therapy

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Introduction/Epidemiology

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. The incidence (626,000 new cases per year) is approximately equivalent to the death rate (598,000), demonstrating the significant lethality of this malignancy.[1] Seventy-five to 80% of HCC cases worldwide are related to persistent viral infections with either Hepatitis B or C.[2] HCC is endemic in sub-Saharan Africa, eastern and southeastern Asia, and Melanesia,[1] and increasing in incidence in the United States and Europe, most likely due to immigration from endemic regions and an increasing incidence of Hepatitis C related cirrhosis.[3] Recently, studies showed that nonalcoholic steatohepatitis (NASH), a well-recognized cause of cirrhosis, is associated also with the development of HCC.[4]

Multiple staging systems have been proposed to predict survival in patients with HCC, none of which have been universally accepted as standard. The most commonly used staging systems are the tumor, node, metastasis system (TNM), Okuda system, CLIP score, Barcelona Clinic Liver Cancer (BCLC) staging system, and the French prognostic classification. The BCLC staging system is used most frequently. Most of these systems incorporate four factors that are recognized as important prognosticators: severity of underlying liver disease, tumor size, invasion into adjacent structures, and the presence of distant metastasis.[5–10] For example, in the BCLC staging system, early stage (A) patients are asymptomatic and have early tumors appropriate for radical therapies; intermediate stage (B) patients are also asymptomatic, but have multinodular tumors; advanced stage (C) patients have symptomatic tumors, vascular invasion, and/or extrahepatic spread; end stage disease patients (D) have a grim prognosis.[5]

Curative treatment options can be used in early stage patients including hepatic resection, local ablative therapy and liver transplantation. Unfortunately, most HCC patients present at intermediate or advanced stages of disease and are not candidates for curative treatment.[11] Palliative therapy, such as transarterial chemoembolization [TACE], local ablation therapy and radioembolization [Therasphere®], and most recently systemic therapy with sorafenib may be considered, and can lead to a tumor response and improvement in survival in select patients.[12–14]

Treatment of advanced HCC is challenging due to the aggressive nature of the tumor and the usual coexistence of hepatic dysfunction. Sorafenib is the first and only systemic agent that has been shown to improve survival over supportive care alone in advanced HCC. This review will explore the data surrounding the efficacy of sorafenib in various clinical settings, dose modification and the management of toxicities, and the promise of new therapeutic agents.

The advent of sorafenib

HCC is relatively refractory to chemotherapy. Conventional agents have not been shown to improve survival when compared to supportive care alone.[15] Other agents such as tamoxifen, octreotide, and interferon-α have also failed to demonstrate a survival benefit.[15] Effective systemic therapies are therefore desperately needed. Underlying cirrhosis and hepatic dysfunction—present in the majority of HCC patients—limits the safe use of existing agents as well as the development of new systemic therapies.

Prior to the introduction of sorafenib in 2008, chemoembolization was the only treatment shown to improve survival in patients with advanced disease.[14,15] Interest in targeted therapy was prompted by a better understanding of the molecular pathways involved in hepatic carcinonogenesis. Preclinical studies have shown that the activation of signaling cascades involving Ras/Raf/MAPK plays an important role in the growth and survival of HCC cells.[16] HCV-infected cells have a high basal expression of Raf-1, which may increase the risk of neoplastic transformation.[17,18] In addition, HCC is typically a hypervascular tumor with increased expression of vascular endothelial growth factor (VEGF).[19,20] Sorafenib is a multikinase inhibitor that blocks tumor proliferation by targeting the RAF/MEK/ERK signaling pathway and multiple tyrosine kinases involved in angiogenesis and proliferation, including vascular endothelial growth factor receptor (VEGFR-2/-3), platelet-derived growth factor receptor β, Flt-3, and c-KIT.[21]

In a phase II study in 2006, patients with advanced HCC and Child-Pugh scores of A or B treated with sorafenib had an overall survival (OS) of 9.2 months with encouraging prolonged stable disease rate. Toxicities were generally manageable and included hand-foot skin reaction (5.1%), fatigue (9.5%), and

diarrhea (8.0%). There were no reported Grade IV toxicities.[22] One study participant died of an intracranial hemorrhage, however it is unclear whether this death was drug-related.[22]

A phase III trial (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol, or SHARP) included 602 participants from Europe, North America, South America, and Australia with advanced HCC and Child-Pugh scores of A who were randomly assigned to receive sorafenib or placebo. OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR 0.69; 95% CI: 0.55 to 0.87; P value < 0.001). Tumor response was minimal—2% of patients in the sorafenib group had a partial response compared to 1% in the placebo group. No patients had a complete response. Grade III toxicities in the sorafenib group included diarrhea (8%), hand-foot reaction (8%), hypertension (2%), and abdominal pain (2%). Laboratory abnormalities included grade III hypophosphatemia (11%) and grade III/IV thrombocytopenia (4%). The incidence of serious hepatobiliary adverse events (eg, variceal bleeding) was similar in both groups.[12] This study established sorafenib as the standard of care for advanced HCC, and it remains the only systemic therapy approved by the FDA.

In a second randomized controlled trial with participants from China, South Korea and Taiwan, sorafenib was superior to placebo in OS (6.5 months vs. 4.2 months; HR 0.68; 95% CI: 0.50–0.93; P value 0.014). However, survival in both arms was worse than in the respective arms of the SHARP trial. Eligibility criteria were similar, but participants in the Asian study were more likely to have had extrahepatic spread, a greater number of hepatic lesions, poorer ECOG performance status, and increased serum alpha-fetoprotein (AFP) levels. Also, 73.5% of patients in the Asian study had underlying HBV infection (which may be associated with poorer prognosis than HCV infection), compared to only 18% in the SHARP trial. Grade III/IV toxicities included hand-foot reaction (10.7%), diarrhea (6%), fatigue (3.4%), and hypertension (2%). As in the SHARP trial, serious hepatobiliary events were similar in both arms.[13] A comparison of both the SHARP trial and the Asian study is outlined in Table 1. In a subgroup analysis of the SHARP trial, participants with HCV infection had an overall survival of 14 months in the sorafenib group versus 7.9 months in the placebo group (HR; 0.58; 95% CI: 0.37–0.91), providing further evidence that prognosis may be superior in HCV associated HCC compared to HCC secondary to other etiologies.[23]

Neither phase III trials demonstrated significant tumor response to sorafenib, suggesting that response

Table 1. Comparison of SHARP and Asian study.

	SHARP	Asian study
Participants	602	226
Geographic region	Europe/Australasia/America	China/Taiwan/South Korea
Median age	65	51
Male	87%	85%
Child-Pugh class A	97%	97%
ECOG PFS 0/1/2	54%/38.5%/7.5%	26%/68%/5.3%
Macroscopic vascular invasion	38%	35%
Extrahepatic spread		
Lymph nodes	26%	32%
Lungs	21%	50%
BCLC stage C	82.5%	95.5%
Hepatitis virus status		
HBV infection	18%	73%
HCV infection	28%	8%
RR (Sorafenib/placebo)	2%/1%	3.3%/1.3%
TTP (Sorafenib/placebo)	5.5 months/2.8 months	2.8 months/1.4 months
HR	0.58 (95% CI: 0.45–0.74)	0.57 (95% CI: 0.42–0.79)
OS (Sorafenib/placebo)	10.7 months/7.9 months	6.5 months/4.2 months
HR	0.69 (95% CI: 0.55–0.87)	0.68 (95% CI: 0.50–0.93)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer Staging System; PFS, performance status; RR, response rate; TTP, time to progression; HR, hazard ratio; OS, overall survival.

is not a good surrogate for survival in HCC. Sorafenib may improve survival solely by preventing tumor progression. It is also possible that standard methods for evaluating tumor response are not appropriate in HCC. In both the SHARP and Asian trials, response was measured using RECIST criteria (Response Evaluation Criteria in Solid Tumors), which involves measurement of radiographic changes in tumor diameter.[24] Two studies have questioned whether tumor response should be evaluated this way in HCC. Both investigated the use of cisplatin, doxorubicin, 5-fluorouracil, and interferon-α. Some participants who only achieved a partial radiographic response later underwent surgery and were found to have had a complete pathologic response.[25,26]

While sorafenib is now the standard of care for advanced HCC patients with a Child-Pugh score of A, its efficacy in those with more advanced liver failure is still currently unknown. There has been limited information about the medication in Child-Pugh B patients, data from the initial phase II study suggest that pharmakokinetics and toxicity profiles are similar in Child-Pugh A and B populations.[22] The safety in Child-Pugh C patients is unknown, and due to their extremely poor prognosis, sorafenib is unlikely to be of any clinical benefit.[27,28] Sorafenib also appears to be safe in patients who have relapsed following a liver transplant, however dose reduction is often necessary.[29]

Despite the low toxicity profiles demonstrated in both phase III trials, the dose of sorafenib used in both studies (400 mg twice daily) is hard to maintain in most patients. Unfortunately, there are no clear guidelines regarding the dosing of the medication, duration of therapy, and modification based on patients liver function/treatment related toxicity. At our institution, we start patients on 200 mg twice daily initially with clearly following-up, if patients tolerate the medication well in 1–2 weeks, we will then escalate the dose up to the suggested dose. Interestingly, interim data from an ongoing global prospective non-interventional registry study suggests differential use of sorafenib by medical specialties. It appears that oncologists tend to treat with lower doses and for a somewhat shorter duration than hepatologist and/or gastroenterologists.[30]

Combination therapy

It is unclear whether there is a benefit to combining sorafenib with other treatments. Two published studies have examined the use of sorafenib in combination with chemotherapy in advanced HCC. One phase II trial compared the use of doxorubicin with or without sorafenib. Progression free survival (PFS) and overall survival (OS) were superior in the arm receiving combined therapy (PFS 6.0 months (95% CI 4.6–8.6) versus 2.7 months (95% CI 1.4–2.8), *P* value 0.006; OS 13.7 months (95% CI, 8.9-not reached) versus 6.5 months (95% CI, 4.5–9.9), *P* value 0.006).[31] A phase II trial performed in Taiwan examined the use of an oral fluoropyrimidine, tegafur/uracil, in combination with sorafenib. Median PFS was 3.7 months (95% C.I, 1.9–5.5), and median OS was 7.4 months (95% C.I, 3.4–11.4). Seventy-two percent of study participants were Hepatitis B surface antigen-positive.[32] Preliminary results of a phase II trial investigating sorafenib combined with infusional 5-Fluorouracil were presented by Petrini et al at ASCO 2009. Time to progression (TTP) was 7.6 months (CI 95%, 5.3–9.9) and OS 12.2 months (CI 95%, 4.45–19.8).[33] In all studies, the combination of chemotherapy with sorafenib was considered safe and feasible.

Sorafenib has only been approved for the treatment of advanced HCC, however, there is much interest in determining whether it has a role in earlier stages of disease. The STORM trial is a phase III study investigating the use of sorafenib as adjuvant therapy. Patients who undergo surgical resection or local ablation with curative intent are randomized to receive sorafenib 400 mg twice daily or placebo. This study is ongoing (Clinicaltrials.gov identifier: NCT00692770).

Additional studies are investigating the use of sorafenib in combination with transarterial chemoembolization (TACE)—a local therapy shown to improve survival in patients with intermediate stage HCC.[14] TACE involves obstruction of a portion of the hepatic artery which leads to necrosis of the highly vascularized tumor. Embolization agents are mixed with chemotherapeutic agents, most commonly cisplatin, mitomycin, and doxorubicin administered alone or in combination. Only select patients with preserved liver function and no evidence of vascular invasion or extrahepatic spread are candidates for TACE. Currently, sorafenib is only considered when TACE is not (or is no longer) an option. However, a phase I study examined the administration of continuous sorafenib

(400 mg twice daily) starting 7 days prior to TACE and continued until progression or treatment intolerance. Toxicities were similar to those seen with sorafenib monotherapy, except for a higher frequency of thrombocytopenia (21%).[34] One phase III study which randomized patients to sorafenib or placebo after TACE did not detect a difference in time to progression (TTP) between the two arms. Forty-one percent of participants in the sorafenib arm discontinued the drug due to adverse events (compared to 6% in the placebo arm).[35] There are currently multiple ongoing trials further investigating the efficacy and safety of the combination of TACE and sorafenib, including the large phase II SPACE study (Clinicaltrials.gov identifier: NCT00855218).

New Agents

Sunitinib

Sunitinib is a multikinase inhibitor that is approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors. There are three phase II studies that have examined its role as front-line oral therapy in patients with advanced HCC and Child-Pugh scores of A or B:

- Faivre et al studied patients taking sunitinib 50 mg daily for four weeks out of a six week cycle. As with sorafenib, the response rate was low at 2.9% (95% CI, 0.1–14.2), however PFS was 3.7 months (95% CI, 1.8–6.5) and OS was 8.0 months (95% CI, 4.4–13.1). Unfortunately, grade III/IV toxicities were not rare, the most common being thrombocytopenia and neutropenia. Four deaths that occurred on study were possibly treatment-related.[36]
- Zhu et al studied patient taking sunitinib 37.5 mg daily for four weeks out of a six week cycle. The response rate was 2.9% (95% CI, 0.2% to 14.9%). PFS was 3.9 months (95% CI, 2.6 to 6.9 months) and OS was 9.8 months (95% CI, 7.4 months to not reached). Grade III/IV toxicities were not as common as in the study by Faivre.[37]
- Koeberle et al studied patients taking sunitinib 37.5 mg per day continuously. PFS was 1.5 months (95% CI, 1.38–2.83) and OS was 9.3 months (95% CI, 5.6–12.9 months).[38]

From these three trials, it appears that the smaller dose of sunitinib decreases toxicity without compromising efficacy. The smaller OS observed by Faivre et al may be due to a greater proportion of patients with Hepatitis B in the study population.[36–38] The OS in these three trials was similar to that in the original sorafenib phase II trial,[22] however with slightly more hematologic toxicity. Unfortunately, a phase III trial comparing sorafenib with sunitinib was terminated early in April 2010 due to increased toxicity in the sunitinib arm and failure to demonstrate superior or non-inferior survival (http://clinicaltrials.gov/ct2/show/NCT00699374).

A retrospective analysis by Worns et al examined the use of sunitinib after progression on sorafenib. OS was 8.4 months from the initiation of sunitinib and 19.3 months from the initiation of sorafenib. In two patients, sunitinib was discontinued due to hemorrhagic complications (variceal bleeding and intracranial hemorrhage). Patients with a Child-Pugh score of B did not seem to benefit from the sequential administration of sunitinib.[39] Thus, due to toxicity and unclear efficacy, the role of sunitinib in advanced HCC appears limited.

Bevacizumab

Bevacizumab is a recombinant humanized antibody directed against vascular endothelial growth factor (VEGF) that is a key therapeutic agent in the treatment of metastatic colorectal and lung cancers.[40–42] Bevacizumab's anti-tumor activity is thought to be the result of impaired tumor angiogenesis and decreased tumor interstitial pressure which may allow better drug delivery to the tumor.[43,44] For these reasons, bevacizumab may be a promising therapy for the treatment of HCC, which is typically a hypervascular tumor with increased expression of VEGF.[19,20]

One phase II trial by Siegel et al investigated the use of bevacizumab monotherapy (5–10 mg/kg once every two weeks) in advanced HCC, however only patients with intrahepatic disease were included. Response rate was higher than in the sorafenib trials at 13% (95% CI, 3% to 23%). PFS was 6.9 months (95% CI, 6.5 to 9.1 months) and OS was 12.4 months (95% CI, 9.4 to 19.9 months). Four patients eventually underwent liver transplantation. Grade III/IV bleeding occurred in 11% of participants, with one patient dying of a variceal bleed.[45]

Bevacizumab has also been studied in combination with chemotherapeutic agents in advanced HCC:

- Zhu et al investigated bevacizumab in combination with gemcitabine and oxaliplatin. The objective response rate was 20%, PFS was 5.3 months (95% CI, 3.7 to 8.7 months), and OS was 9.6 months (95% CI, 8.0 months to not available). Six percent (2/33) had upper GI bleeding, and 3% (1/33) experienced grade III epistaxis.
- Sun et al examined bevacizumab in combination with capecitabine and oxaliplatin and showed a response rate of 20% with disease control rate of 77.5% (PR + SD) and PFS of 6.8 months. Two of 40 participants had variceal bleeding, and one had a GI perforation with resultant sepsis.[46]
- An Asian study investigating the combination of bevacizumab and capecitabine reported a response rate of 9%, PFS of 2.7 months (95% CI: 1.5–4.1 months), and OS of 5.9 months (95% CI: 4.1–9.7 months). Nine percent of patients (4/43) experienced a GI bleed while on therapy.[47]
- A phase II study examined Erlotinib, an endothelial growth factor receptor (EGFR) tyrosine kinase inhibitor, in combination with bevacizumab. Response rate was 25%, PFS was 9.0 months (95% CI, 26 to 45 weeks), and OS was 15.7 months (95% CI, 48 to 78 weeks). Five out of 40 (12.5%) participants experienced a gastrointestinal hemorrhage while on therapy.[48]
- Finally, bevacizumab has been combined with chemotherapy (Capecitabine, CAPOX, and GemOX) in three phase II studies with promising results.[49–51]

In conclusion, bevacizumab may be efficacious in HCC, however confirmation by a large phase III trial is needed. The additional risk of bleeding is concerning in patients with liver disease, and must be weighed carefully against the benefits of the drug.

EGFR Inhibitors

Erlotinib may also have promise in treatment of advanced HCC either as monotherapy or in combination. Two phase II trials examined erlotinib 150 mg once daily. Tumor response was rare, but OS was 13 months and 10.57 months in the two studies. Common toxicities included diarrhea, rash, and fatigue, however overall treatment was well tolerated.[52,53] As stated above, a phase II study showed encouraging results with combination of erlotinib and bevacizumab.[48] A phase III study of erlotinib in combination with sorafenib as first line treatment of advanced HCC is currently underway (Clinicaltrials.gov identifier NCT00901901).

Cetuximab, a monoclonal antibody to EGFR, does not appear to have activity against HCC when used as monotherapy.[54] However, it may have a role in combination with gemcitabine and oxaliplatin.[55] Lapatinib, another small molecule tyrosine kinase inhibitor which targets EGFR and Her2, does not appear to have strong anti-tumor activity in this disease.[56]

Brivanib

Brivanib, an oral inhibitor of both VEGF and fibroblast growth factor (FGF), is another promising agent. Its efficacy as both a first and second line agent for advanced HCC is currently being assessed in a phase II trial. Preliminary results presented at ASCO 2009 showed an OS of 10 months (95% CI: 6.8 months- not reached) for participants receiving brivanib as first line therapy. Brivinib also appeared to have anti-tumor activity when used as a second line agent. Toxicities included fatigue, AST elevation, hyponatremia, diarrhea, headache, and hypertension.[57] In two ongoing phase III trials, brivanib is being compared to sorafenib as first line treatment (Clinicaltrials.gov identifier NCT00858871), to placebo after progression on sorafenib (Clinicaltrials.gov identifier NCT01108705), and to placebo in combination with TACE (Clinicaltrials.gov identifier NCT00908752).

m-TOR inhibitors

Cell growth and proliferation in multiple cancer types are regulated by the mammalian target of rapamycin (m-TOR).[58] The m-TOR pathway is upregulated in HCC, and preclinical studies have shown that m-TOR inhibitors can inhibit proliferation of HCC cell lines,[59] as well as the growth of HCC xenographs in mice.[60,61] Early phase studies suggest that m-TOR inhibitors may have some anti-tumor activity in the clinical setting:

- A pilot study examined the use of sirolimus as first line therapy in 14 patients with advanced HCC. The median duration of treatment was 22 weeks (8–34).

The investigators observed one complete response (7%) and five partial responses (33%). All other patients experienced stable disease for a mean time of 16 weeks. Toxicities were mucositis (35%), asthenia (28%) and skin toxicity (28%).[62]

- A phase I study examining the use of everolimus in advanced HCC showed modest tumor activity with a disease control response (DCR) of 61% when the drug was administered daily and 46.7% when the drug was administered weekly.[63]
- Another phase I/II study examining the use of everolimus in advanced HCC as first, second, or third line therapy showed modest antitumor activity with a TTP of 3.9 months (95% CI: 2.5–5.5), and an OS of 8.4 months (95% CI: 3.9–21.1).[64]

There are multiple ongoing studies further investigating the use of m-TOR inhibitors in advanced HCC. Since m-TOR inhbitors are acceptable forms of immunosuppression used to prevent rejection after a solid organ transplant, there might be benefit to incorporating them into the immunosuppressive regimen after a liver transplant for HCC. In a phase III randomized clinical trial, a sirolimus based regimen is also being compared to other immunosuppressive regimens in this setting. The primary outcome measure is recurrence free survival. This trial is currently ongoing (Clinicaltrials.gov identifier: NCT00355862).

Conclusion

Better understanding of the molecular events involved in hepatic carcinogenesis has led to a new era of targeted therapy for the treatment of advanced HCC. Sorafenib improves survival with an acceptable toxicity profile in patients with advanced/metastatic HCC. More studies are on going to investigate the agent either as combination with other agents for advanced disease or in the adjuvant setting combining with local therapies such as TACE. Phase II studies investigating the use of multiple targeted therapies alone, in combination with other targeted agents, or in combination with conventional chemotherapy have shown promising results, however phase III trials are needed to better establish their safety and efficacy.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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