Development of Molecularly Targeted Therapies in Hepatocellular Carcinoma: Where Do We Go Now?

Richard S. Finn

Abstract

Hepatocellular carcinoma (HCC), once considered an orphan disease in the West, has become a global health concern. It is the third leading cause of cancer death worldwide, and its incidence continues to increase. Historically, the development of new systemic agents for advanced HCC has been lacking despite no clear benefit with traditional cytotoxic therapies. Although two randomized studies with sorafenib for the treatment of HCC patients have recently been completed, survival benefits have been modest and highlight the unmet medical need among patients with HCC. Given the clear need, clinical development of novel systemic agents in HCC has begun in earnest. These clinical studies are founded on a growing body of basic and translational science that has identified several potential molecular targets in HCC. The successful development of such targeted agents in the future will be linked to our ability to appropriately select patients for treatment based on their clinical stage (including extent of liver disease and extent of tumor) and on potential predictive markers of response. Here, we review these data in the context of rational drug development in HCC in the front-line setting and in previously treated patients.

HCC Is Not One Disease

HCC represents two diseases: primary liver dysfunction/cirrhosis and malignancy. The development of new agents for HCC therefore requires consideration of these comorbid conditions, particularly because agents with efficacy against malignant growth may not provide favorable effects on underlying progressive cirrhosis. In HCC tumorigenesis, several oncogenic pathways have been identified. The molecular heterogeneity in pathways that underlie HCC pathogenesis (hepatocarcinogenesis) may affect the success of therapeutic interventions. Several “molecular subtypes” of HCC have been identified, and recent data highlight the interplay between surrounding tissue and the tumor. These studies highlight that hepatocarcinogenesis is a complex process involving hepatocyte injury, inflammation, proliferation, and genomic instability leading to alterations in several oncogenic pathways, such as inactivation of the tumor suppressor p53 and overexpression of various ErbB receptor family members. In addition, new screening approaches, such as RNA interference, have identified novel targets for HCC therapy.

Angiogenesis: vascular endothelial growth factor and fibroblast growth factor. The role of vascular endothelial growth factor (VEGF) in HCC is well established and elevated VEGF receptor (VEGFR) levels and high microvessel density in liver tumors are important for...
Other potential molecular targets in HCC: peptide growth factors and their receptors. Epidermal growth factor receptor (EGFR) is a well-defined pathway of potential interest in HCC. Although elevated levels of EGFR are found in HCC (41), single-agent studies with EGFR-directed therapies (both antibodies and small-molecule tyrosine kinase inhibitors [TKI]) have been disappointing (42–46). Recent preclinical data suggest that only a more “epithelial” subtype of HCC, as defined by the expression of E-cadherin (versus the presence of vimentin and absence of E-cadherin in more “mesenchymal” subtypes), may be dependent on EGFR signaling (47). Similar work has further defined these subgroups using cytokeratin expression (48). These results suggest that, in order for EGFR agents to provide clinical benefit, a specific target population may need to be identified.

Like EGFR, the hepatocyte growth factor and its receptor (HGF/c-Met) have been implicated in HCC (49, 50). Although the clinical efficacy of targeting HGF/c-Met has yet to be determined, several studies with receptor- and ligand-specific antibodies and TKIs are ongoing or in development (51). Recent biomarker data from a phase III sorafenib study identified elevated hepatocyte growth factor levels as a potential predictor of poor prognosis in HCC (52).

The insulin-like growth factor receptor has been implicated in the pathogenesis of several solid tumors, including HCC, providing a possible link between nonalcoholic steatosis and HCC (53). Early studies with insulin-like growth factor receptor–targeted agents have shown activity in Ewing’s sarcoma (54); however, preclinical and clinical data in HCC patients are still evolving. One recent preclinical study reported that NVP-AEW541, a insulin-like growth factor-I receptor TKI, induces growth inhibition, apoptosis, and cell cycle arrest in human HCC cell lines without accompanying cytotoxicity, supporting the rationale for investigating this target further (55).

Intracellular targets. The biological effects of receptor tyrosine kinase activation are mediated by a complex cascade of intracellular signaling molecules that are potential targets for therapy, including the phosphoinositide 3-kinase and the ras/raf/mitogen-activated protein kinase pathways.

Activation of the phosphoinositide 3-kinase pathway results in signaling via AKT and mammalian target of rapamycin (mTOR; ref. 56). Several studies have suggested that increased mTOR activity is associated with outcome in HCC (57–59). mTOR is a potent inducer of angiogenesis via its upregulation of the hypoxia-induced gene HIF1-α (60). The mTOR inhibitors rapamycin (61) and everolimus (RAD001; refs. 59, 62) have shown preclinical activity in HCC. Clinical data suggest that post-transplant patients with HCC who are treated with mTOR inhibitors may have a lower risk of recurrence (63). Finally, preclinical studies have shown additive or synergistic activity between rapamycin and everolimus in combination with sorafenib in HCC (59, 64). Clinical studies to investigate these combinations are clearly warranted.
Mutations in the ras/raf/mitogen-activated protein kinase pathway are common in human tumors (65). Although activating ras mutations have been detected in colon, lung, and pancreatic cancers and activating raf mutations in melanoma (65), nonmutational activation of this pathway has been implicated in HCC. The clinical activity of sorafenib has been linked to increased activation of b-raf, although this has not been validated (66).

Another target is MEK1 and MEK2 (mitogen-activated protein kinase). In mouse models, AZD6244, a noncompetitive inhibitor of MEK1 and MEK2, had potent antiproiferative and proapoptotic effects (62). Clinical studies are beginning with AZD6244 as monotherapy in advanced HCC (NCT00604721).

Survivin expression in HCC is common (40-70%) and has been associated with poor survival (67, 68). Survivin is a protein that functions as a negative regulator of apoptosis, because the protein is intracellular modulation with small molecules are not feasible. In HCC preclinical models, the use of small interfering RNA and antisense oligonucleotide-based approaches to reduce survivin expression has shown some promise (69).

Src is another potential target in HCC. Recent preclinical work with the Src/Abl inhibitor dasatinib suggests that there is a specific molecular subgroup of HCC that may be dependent on Src signaling: this will require clinical validation (70).

The above results across studies reflect the heterogeneity of HCC, which results from the various etiologies of hepatocarcinogenesis as well as the myriad of potential targets.

**Front-Line Therapy for Advanced HCC: Building on Efficacy Data of Sorafenib**

Two randomized, placebo-controlled studies have proven the efficacy of sorafenib in HCC (71, 72). Both studies included patients with compensated liver disease (Child-Pugh A) from either North America/Europe (the SHARP study; ref. 72) or Asia (71) and reported survival advantages of equal magnitude. In the SHARP study, the median overall survival (OS) was 10.7 months with sorafenib versus 7.9 months with placebo (hazard ratio, 0.69; \(P < 0.001\)). There was no significant difference between the two groups in the median time to symptom progression (4.1 months for sorafenib versus 4.9 months with placebo; \(P = 0.77\)), a coprimary endpoint for the study. Median time to radiologic progression was longer with sorafenib (5.5 versus 2.8 months; \(P < 0.001\)). In the Asian study, median OS was prolonged with sorafenib (6.5 versus 4.2 months; hazard ratio, 0.68; \(P = 0.014\)). Median time to progression was longer with sorafenib [2.8 versus 1.4 months; hazard ratio, 0.57 (0.42-0.79); \(P = 0.0005\)]. In both studies, sorafenib had a predictable and manageable side effect profile.

Clinically, these studies provided evidence that systemic agents can affect the natural course of HCC when the competing risk of underlying cirrhosis is minimized by treating patients with well-compensated liver disease. Interestingly, sorafenib improved time to progression and OS without significant clinical responses (defined by Response Evaluation Criteria in Solid Tumors). The effect of sorafenib in patients with less compensated liver disease (Child-Pugh B and C), however, remains to be seen. In practice, this remains an important question, because the majority of patients with advanced HCC have either Child-Pugh B or C cirrhosis. Sorafenib is primarily metabolized in the liver by cytochrome \(P450\) metabolism and glucuronidation; therefore, studies in patients with declining hepatic function are needed (73). In addition, studies are needed to determine the potential for drug-drug interactions if sorafenib is to be used in combination. Of note, although the results from the Asian study mirrored those in the SHARP trial with respect to the observed OS advantage with sorafenib, both the placebo and the sorafenib groups in the Asian study had inferior outcomes compared with SHARP (median OS, 4.2 and 6.5 months, respectively). This may be explained by differences in the proportion of patients with hepatitis B and C in each study where \(\sim 75\%\) of patients in the Asian study had hepatitis B versus \(\sim 7\%\) had hepatitis C. In contrast, 19% and 28% of patients in the SHARP study had hepatitis B and C as the underlying etiology. These results reinforce the heterogeneity of HCC due in part to the various etiologic factors and highlight the effect of tumor and clinical heterogeneity on the reproducibility of results with the same agent between studies.

Selected targeted agents that are approved or in development are listed in Table 1. Before the approval of sorafenib, several agents with various mechanisms of action were evaluated in HCC in the front-line setting with mixed results. The majority of these studies were single-arm phase II designs. These single-arm studies are difficult to interpret in comparison with the SHARP data, as they do not control for the extent ("stage") of liver disease. An overview of many of the phase II and III proof-of-concept studies with targeted therapies in HCC is given in Table 2. Because of the demonstrated efficacy and recent approval of sorafenib, the future landscape for randomized phase II and III studies will be based on head-to-head comparisons with sorafenib.

**Monotherapy and combination therapy**

**Sunitinib.** Sunitinib is currently being compared with sorafenib in HCC patients in a phase III randomized study (Clinicaltrials.gov NCT00699374). There is limited monotherapy experience with sunitinib in HCC (Table 2). Although it has a some similar molecular targets of sorafenib, it appears to have a different toxicity profile associated with more fatigue and bone marrow suppression (74).

**Bevacizumab plus erlotinib.** As seen in preclinical models with dual inhibition of FGF and VEGF, there may be more promise in combining agents that inhibit both VEGF and EGFR pathways. Monotherapy studies in HCC with EGFR-targeted antibodies (such as cetuximab) and TKIs (such as gefitinib, erlotinib, and lapatinib) have
not shown robust clinical activity (Table 2). The reason for this may be the lack of true “dependence” on EGFR signaling in HCC, the lack of predictive marker for EGFR dependency in a subgroup of HCC, or factors related to patient selection and underlying liver disease. The recently published single-arm, single-institution phase II study of combination therapy with bevacizumab and erlotinib has gained considerable attention (75). This study showed that, in 40 patients with advanced HCC, combination therapy showed antitumor activity, with progression-free survival at week 16 in 62.5% of patients, with 10 patients achieving partial responses for a confirmed overall response rate of 25%. An updated analysis in 58 patients reported an overall response rate of 28% and 16-week progression-free survival of 72% (76). This approach is now being evaluated in two studies in the front-line setting (NCT003653391 and NCT00881751). One, a phase II study, will compare bevacizumab and erlotinib versus sorafenib alone in a similar population as in the SHARP study, and the second, a phase III study, will compare erlotinib and sorafenib versus sorafenib alone. The safety and efficacy of bevacizumab and erlotinib is also being investigated in an ongoing study in Asian patients with advanced HCC (77). A recent interim analysis of safety data from this trial reported that, of the 51 enrolled patients, 2 patients had confirmed partial responses for a confirmed overall response rate of 25%. Although not randomized, these data are promising and compare favorably with the results of sorafenib in an Asian Pacific population (71).

**Brivanib.** Brivanib has shown activity in mouse models of human HCC (77). Interim analyses from a study of single-agent brivanib as first- and second-line therapy showed that, in a largely Asian population of 55 patients with advanced HCC, first-line treatment with brivanib was associated with a median time to progression of 2.8 months, with a disease control rate of 60% (47 evaluable patients) and median OS of 10 months (79).

### Traditional cytotoxic agents: combination with targeted agents

Studies with cytotoxics as single agents or in combination have not shown any survival advantage in HCC (81). In other tumor types, targeted agents that do not have significant activity as monotherapy may have the ability to markedly increase the efficacy of active chemotherapy regimens and improve OS (82).

In HCC, a randomized phase II study of doxorubicin and sorafenib versus doxorubicin alone in the front-line setting improved median survival from 6.5 to 13.7 months, although the study was not designed to detect differences between treatments (83). Although a randomized study is required to investigate activity further, contrary to expectations, given the known activity of these drugs as single agents, there was not an increase in response rate with the combination. These data also raised some concern regarding the cardiotoxicity of the combination, as there was an apparent increase in cardiac adverse events with the combination. Single-arm, open-label studies combining bevacizumab and chemotherapy have been completed (84), and although these studies can be interpreted as showing promising clinical activity, randomized studies are required to show and validate clinical efficacy.

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**Table 1. Comparison of selected targeted agents that are approved or currently in development**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Mechanism of action</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib*</td>
<td>Small molecule</td>
<td>TKI</td>
<td>VEGFR2, VEGFR3, PDGFR, Flt-3, c-Kit, and raf</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal antibody</td>
<td>Blocks VEGF binding to its receptor</td>
<td>VEGF</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Small molecule</td>
<td>TKI</td>
<td>VEGFR1, VEGFR2, PDGFR, c-Kit, Flt-3, and ret</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Small molecule</td>
<td>TKI</td>
<td>EGFR</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Small molecule</td>
<td>TKI</td>
<td>EGFR</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Monoclonal antibody</td>
<td>Blocks EGFR binding to receptor</td>
<td>EGFR</td>
</tr>
<tr>
<td>Brivanib</td>
<td>Small molecule</td>
<td>TKI</td>
<td>VEGFR1 to VEGFR3, FGFR1 to FGFR3</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Small molecule</td>
<td>TKI</td>
<td>EGFR, HER-2/neu</td>
</tr>
</tbody>
</table>

*Approved in HCC.
Second-Line Therapy for Advanced HCC: A New Patient Population

Treatment of patients with HCC progressing during sorafenib treatment has now become another challenge. The laboratory and preclinical work reviewed here can provide insight into new targets for therapy, but the exact mechanisms of both acquired and de novo resistance to sorafenib are still unknown. Further, it is difficult to associate any single genetic alteration with a specific etiology of HCC, making patient selection for novel therapeutics on clinical grounds difficult. Although difficult to do in HCC, as many patients do not undergo a routine biopsy for diagnosis, biomarker studies will ultimately be required to define these mechanisms and guide the next generation of targeted agents.

Recent preliminary data have shown that brivanib as a single agent had a clear therapeutic signal in patients who progressed following one prior antiangiogenic agent (sorafenib or thalidomide in small number of patients). 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 time to progression of 2.7 months, and a median OS of 9.8 months. Brivanib was well tolerated, the most common adverse events being fatigue and diarrhea of generally Common Toxicity Criteria grade 1 or 2 (79). As described earlier, laboratory data suggest that FGF signaling is able to mediate resistance to VEGF-targeted therapies, and its ability to block FGFR signaling is one possible mechanism for the activity of brivanib in the second-line setting, whether de novo resistance or acquired.

This hypothesis is being further evaluated in the BRISK program in a placebo-controlled brivanib phase III study in HCC patients with disease that has progressed with sorafenib or who cannot tolerate sorafenib in the front-line setting (NCT00858871; BRISK PS). In addition, patients progressing on sorafenib with preserved liver function may be candidates for phase I studies evaluating new agents.

Table 2. Overview of completed and ongoing phase II and III studies with targeted therapies in HCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>Sample size</th>
<th>Response rate (%)</th>
<th>Progression-free survival/time to progression (mo)</th>
<th>Median survival (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>3</td>
<td>300</td>
<td>2.3</td>
<td>5.5 (T)</td>
<td>10.7 (vs 7.9 placebo)</td>
<td>Llovet et al. (72)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3</td>
<td>271</td>
<td>2.8</td>
<td>2.8 (T)</td>
<td>6.5 (vs 4.2 placebo)</td>
<td>Cheng et al. (71)</td>
</tr>
<tr>
<td>Sorafenib + doxorubicin</td>
<td>2</td>
<td>47</td>
<td>4</td>
<td>8.6 (T)</td>
<td>13.7 (vs 6.5 placebo)</td>
<td>Abou-Alfa et al. (83)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2</td>
<td>37</td>
<td>2.7</td>
<td>5.2 (P)</td>
<td>11.2</td>
<td>Faire et al. (88)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2</td>
<td>34</td>
<td>2.9</td>
<td>3.9 (P)</td>
<td>9.8</td>
<td>Zhu et al. (74)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2</td>
<td>38</td>
<td>9</td>
<td>3.2 (P)</td>
<td>13</td>
<td>Philip et al. (89)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2</td>
<td>40</td>
<td>0</td>
<td>3.1 (P)</td>
<td>6.3</td>
<td>Thomas et al. (43)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>2.8 (P)</td>
<td>6.5</td>
<td>O’Dwyer et al. (90)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>2</td>
<td>30</td>
<td>0</td>
<td>1.4 (P)</td>
<td>9.6</td>
<td>Zhu et al. (45)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2</td>
<td>32</td>
<td>0</td>
<td>1.87 (T)</td>
<td>—</td>
<td>Gruenwald et al. (91)</td>
</tr>
<tr>
<td>Bevacizumab + erlotinib</td>
<td>2</td>
<td>46</td>
<td>13</td>
<td>6.9 (P)</td>
<td>12.4</td>
<td>Siegel et al. (92)</td>
</tr>
<tr>
<td>Bevacizumab + gemcitabine + oxalaplatin</td>
<td>2</td>
<td>40 25 5.3 (P)</td>
<td>9 (P)</td>
<td>15.65 Thomas et al. (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivanib</td>
<td>2</td>
<td>55</td>
<td>2.8 (T)</td>
<td>10</td>
<td></td>
<td>Finn et al. (80)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2</td>
<td>46</td>
<td>2.7 (T)</td>
<td>9.8</td>
<td></td>
<td>Bekaii-Saab et al. (46)</td>
</tr>
</tbody>
</table>

NOTE: P refers to progression-free survival, whereas T refers to time to progression.
For combination studies, a recent phase II study investigated bevacizumab in combination with erlotinib in patients with advanced HCC as first- and second-line therapy. Here, eight patients received the combination as second-line post-sorafenib treatment with a progression-free survival of 7.9 months and OS of 13.3 months. Tolerability was not reported, but a further study is planned to investigate this combination (76).

Intermediate-Stage Patients: Improving on Locoregional Therapy

The greatest effect on survival in HCC may come from initiating treatment at earlier disease stages. A large percentage of patients with HCC present with disease confined to the liver and adequate liver function. In this group (Barcelona Clinic Liver Cancer Stage B), TACE has become the backbone of management. Although the exact chemotherapy regimen employed in TACE and its delivery varies geographically, it is clear that there is a subset of patients who remain refractory to TACE; however, even those patients who do gain some initial benefit eventually progress. Conceptually, the addition of a systemic antiangiogenic agent to TACE makes clinical sense. In a small randomized pilot study evaluating TACE with or without bevacizumab, a decrease in neovascularization with the addition of bevacizumab was observed along with a decrease in the usual post-TACE increase in VEGF (85). Other early reports from ongoing studies have shown that adding sorafenib to TACE is safe, but efficacy data are still awaited from several prospective studies [e.g., NCT00576056 and NCT00855218 (SPACE)].

Post hoc subanalyses from the SHARP study suggest that the benefit from sorafenib may be greater in those patients without overt metastatic disease (86, 87). Studies evaluating sorafenib in the post-ablation or resection population (the STORM study; NCT00692770) or post-transplant setting are ongoing. Based on a similar rationale and the potential added benefit of FGFR inhibition, a phase III placebo-controlled study evaluating brivanib in combination with TACE is currently planned (NCT00908752; BRISK TA) and will evaluate the effect of brivanib on OS in patients with intermediate-stage HCC undergoing TACE.

Conclusion

HCC is a disease that is growing in prevalence due to the increased global incidence of hepatitis. Nonetheless, it is treatable, and several studies are investigating new molecular targets that are involved in HCC pathogenesis. Antiangiogenic strategies are likely to continue to be important in HCC treatment, particularly in terms of multitargeted compounds and in combination therapy. An understanding of mechanisms of resistance to VEGF therapies will pave the way for effective second-line therapies and more efficacious front-line regimens. Although sorafenib has shown a modest survival benefit for patients with early disease, more is needed for patients with advanced and treatment-resistant HCC to improve clinical outcomes. Clinical benefits such as seen with brivanib in the first-line setting and after sorafenib highlight the potential to improve the clinical course of patients with advanced HCC. Newer agents will provide an option for the growing population of patients for whom no other treatment choices exist. Successful clinical development of new agents will require careful patient selection based on both stage of underlying liver disease and tumor burden. Finally, analyses are defining the molecular heterogeneity of HCC and will eventually lead to the identification of clinically useful biomarkers that are both prognostic and predictive of response to novel therapeutics.

Disclosure of Potential Conflicts of Interest

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References


Correction: Development of Molecularly Targeted Therapies in Hepatocellular Carcinoma: Where Do We Go Now?

In this article (Clin Cancer Res 2010;16:390–7), which was published in the January 15, 2010, issue of Clinical Cancer Research (1), there was an error in the median survival column in Table 2. The value for brivanib was misaligned and should have appeared as two values: 10 in the “First-line” row and 9.8 in the “Second-line” row. The online article has been changed to reflect this correction and no longer matches the print.

Reference


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