Selection of Patients with Hepatocellular Carcinoma for Sorafenib

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Abstract
Sorafenib, a multitargeted anti-vascular endothelial growth factor (VEGF) receptor and raf kinase inhibitor, was recently approved by the FDA for treating unresectable hepatocellular carcinoma (HCC) based on 2 randomized phase III studies. In addition, a phase II study evaluating sorafenib in patients with HCC and Child-Pugh A and B and a phase I study evaluating sorafenib in patients with organ dysfunction have provided insight about the safety and efficacy of sorafenib in patients with HCC and more advanced cirrhosis, and any difference in outcome based on etiology of HCC. The lack of objective responses observed in the sorafenib arm in the SHARP study also raises practical issues about how to assess response or efficacy of the therapy and thus how long a patient should receive sorafenib. This article addresses these questions on the use of sorafenib in HCC, both in the locally advanced and metastatic settings, in addition to the potential future applications and uses of sorafenib. (JNCCN 2009;7:397–403)

Sorafenib, a multitargeted anti-vascular endothelial growth factor (VEGF) receptor and raf kinase inhibitor, was recently approved by the FDA for treating unresectable hepatocellular carcinoma (HCC). The approval was based on a large, double-blinded, randomized phase III trial (SHARP trial) evaluating single-agent sorafenib versus placebo in patients with advanced HCC and Child-Pugh A cirrhosis. Patients with more severe cirrhosis were excluded. This trial showed an improvement in survival of 10.7 months in the sorafenib group versus 7.9 months in the placebo group (P < .001; HR = 0.69). The FDA label was not specific about patient selection for sorafenib use. Subgroup analyses of the phase II and III studies of sorafenib in HCC have implied an improved benefit of sorafenib in patients with hepatitis C–induced HCC versus HCC induced by other causes. A more recent randomized phase III trial from the Asia-Pacific region involving patients with a more advanced-stage disease induced mainly by hepatitis B showed that, compared with placebo, sorafenib had a survival advantage of the same statistical significance as the SHARP trial (HR, 0.68; 95% CI, 0.50–0.93; P = .014), but not to the same magnitude (6.5 vs. 4.2 months; P = .014). Sorafenib has now been widely studied in patients with HCC, including in a phase II study evaluating sorafenib in patients with HCC and Child-Pugh A and B, and a phase I study evaluating sorafenib in patients with organ dysfunction. These studies provide some limited insights about the safety and efficacy of sorafenib in patients with HCC and more-advanced cirrhosis. The lack of objective responses observed in the sorafenib arm of the SHARP study also raises practical issues about how to assess response or efficacy of the therapy and thus how long a patient should receive sorafenib. This article addresses these questions about the use of sorafenib in HCC, in addition to the potential future applications and uses of sorafenib.

This article addresses 4 important questions about the use of sorafenib in HCC: 1) what is the role of local therapies in locally advanced unresectable HCC?, 2) is the outcome different based on whether HCC is caused by hepatitis C or B?, 3) what data are available on safety and efficacy of sorafenib in patients with HCC and more advanced cirrhosis?, and 4) how long should patients continue on therapy given the lack of validated measures to assess response or efficacy? Future directions in the treatment of advanced HCC and other applications of sorafenib in HCC are also discussed.
What is the Role of Local Therapies in Locally Advanced Unresectable HCC?

Sorafenib is the first drug in the modern era to receive FDA approval and be added to the rather empty armamentarium of systemic therapy for HCC after a long, frustrating 30 years of testing chemotherapy as single agents and in combination without any clear improvement in survival, despite some occasional notable responses.5

The most studied older chemotherapy agent is doxorubicin, which over 30 years has generated much debate regarding its efficacy in the treatment of HCC. An initial phase II study, reported in a different era and without definition of “response,” showed a response rate of 79%.9 This small, uncontrolled trial has been followed by many other trials, although none have been able to reproduce anything close to this high response rate.10–15 A recent study compared single-agent doxorubicin with a combination of cisplatin, interferon, doxorubicin, and 5-fluorouracil (PIAF), which, despite an improvement in response (10% for doxorubicin vs. 21% for PIAF) failed to show an improvement in survival (6.8 vs. 8.6 months, respectively; P = .83).16

These frustrating efforts not only opened the door for evaluating novel therapies in HCC but also strengthened interest in local therapies. Two clinical trials17,18 reported a survival advantage for transarterial chemoembolization (TACE) versus symptomatic treatment. However, this positive outcome was not reproduced in other trials.19–22 Bland transarterial embolization (TAE) also never showed a survival advantage.23,24 In addition, no study has shown a difference in survival between patients treated with TAE and TACE. A meta-analysis of randomized controlled trials between 1980 and 2000 including 2466 patients25 concluded that TACE significantly reduces overall 2-year mortality but that TACE was not more effective than TAE. The most recent, and frequently cited, randomized controlled study comparing TACE, TAE, and supportive care26 again showed that TACE had a survival advantage over supportive care. Two less recent meta-analyses27,28 reported no survival advantage for different forms of local therapies, including TACE. Despite this lack of data, chemoembolization with lipiodol or with cytotoxic agents has become accepted worldwide as an important treatment option for patients with unresectable HCC.

Undoubtedly the initial use of sorafenib versus local therapy will remain debatable, especially for cases of locally advanced disease in which TAE or TACE may be appropriate based on the extent of disease, but for which systemic therapy, such as sorafenib, may not seem to deliver the gratifying effect of embolization in patients who still have no distant metastatic disease. This determination will be made based on the clinical judgment and intuition of physicians, preferably those working in the collaborative context of a multidisciplinary group.

Future studies may propose a marriage rather than a divorce between these 2 therapeutic approaches. Preclinical studies have shown that embolizing liver lesions may elicit an angiogenic drive that can cause progression of cancer that might be present at other untreated sites of the liver.29 Hence, a logical argument could be made to investigate adding an antiangiogenic agent to embolization-based approaches. Administering sorafenib after or during TAE or TACE therapy is worthy of study,30 and 2 separate clinical trials are currently investigating this approach with TACE. Maximizing the use of TACE or TAE plus sorafenib in the metastatic setting is also being considered.

For now, this approach remains investigational, and embolization and sorafenib should not be delivered simultaneously, except with a wide time margin of safety considering the low but serious risk for bleeding associated with sorafenib. The transient increase in liver function tests post-TACE should also be considered before starting sorafenib therapy.

Difference in Outcome Based on Etiology of HCC: Hepatitis C versus B?

In the recently reported randomized phase III study evaluating sorafenib compared with placebo in southeast Asian countries,5 a statistically significant improvement (P = .014) in survival was again noted to favor sorafenib (6.5 months) versus placebo (4.2 months), but not to the same magnitude of the SHARP trial. Notably, patients accrued in the Asian study were more ill at start of therapy than those in the SHARP trial (Presented at ASCO 2008, Ll-ovet J), with a generally worse performance status and more advanced stage of disease. These observations may partly or fully explain the difference in magnitude of benefit from sorafenib between those
populations. Notably, the hazard odds ratios were remarkably similar between the studies for overall survival, time to progression, and progression-free survival. These findings suggest that the benefit for sorafenib was observed earlier in the natural history of the disease in the SHARP trial, and a snapshot at median overall survival, time to progression, and progression-free survival was taken earlier compared with the Asia-Pacific study.

The impact of hepatitis on sorafenib treatment in the Asia-Pacific study has not been addressed. In this study, 73% of patients accrued had hepatitis B as an underlying risk factor, versus 18% of patients in the SHARP trial. Results of the SHARP trial suggest that patients with hepatitis C may have an added survival advantage associated with sorafenib therapy. A subgroup analysis of patients with hepatitis C–based HCC noted that those treated with sorafenib (n = 93) had a median survival advantage of 14 months compared with the whole sorafenib-treated group (10.7 months). In contrast, the placebo-controlled hepatitis C group did not have any added survival advantage over the placebo group, suggesting a possible positive influence of hepatitis C status on the efficacy of sorafenib. Notably, the outcome of the 18% of patients with hepatitis B in the SHARP trial remains to be reported.

A retrospective evaluation of the phase II trial evaluating sorafenib in patients with advanced HCC noted that those infected with hepatitis C but not B (n = 13) had a longer time to progression compared with those infected with hepatitis B, but not C (n = 33; 6.5 vs. 4 months, respectively; P = .05). Similarly, patients with hepatitis C showed a trend toward a survival advantage compared with those with hepatitis B (12.4 vs. 7.3 months, respectively; P = .29). However, the small sample size makes definitive conclusions impossible. Of interest, however, is that the hepatitis C virus (HCV)-1 core protein has been associated with an increase in raf kinase activity, suggesting a putative mechanism of preferential activity of sorafenib in patients with HCC of HCV origin, if this preferential activity in fact exists.

This finding, of course, does not undermine the antiangiogenic main effect of sorafenib, and although the drug may seem to have a differential improvement in outcome in patients with different viral hepatitis etiology, the drug remains indicated for all appropriate patients with unresectable HCC regardless of the origin of their cancer, although the relative magnitude of benefit may differ. Currently no data exist on any different outcome on sorafenib in patients with HCC of other origins, including alcohol cirrhosis and nonalcoholic steatohepatitis.

What Data are Available on Safety and Efficacy of Sorafenib in Patients With HCC With More Advanced Cirrhosis?

The results of the SHARP trial apply to patients with good to excellent performance status and Child-Pugh A score. Although this encompasses a subset of patients seen by oncologists, the safety and efficacy of sorafenib in patients with Child-Pugh B or C cirrhosis has not yet been defined and must be further evaluated. In a phase II study evaluating sorafenib in HCC, 28% of patients had Child-Pugh B cirrhosis. Pharmacokinetics for sorafenib were evaluated in 28 patients in the study and the area under the curve over 8 hours (mg.h/L) was comparable between patients with Child-Pugh A (25.4) and those with B (30.3). Maximum concentration (mg/L) was 4.9 and 6 in patients with Child-Pugh A and B, respectively, with similar drug-related toxicity profiles.

However, patients with Child-Pugh B were subsequently observed to experience worsening of liver function more frequently. An increase in bilirubin (all grades based on National Cancer Institute Common Toxicity Criteria version 3.0) was reported in 40% of patients with Child-Pugh B compared with 18% of those with Child-Pugh A. Among patients with Child-Pugh B, 18% developed or had worsening ascites compared with 11% of those with Child-Pugh A. Emerging or worsening encephalopathy was reported in 11% of patients with Child-Pugh B compared with 2% of those with Child-Pugh A. Again, the small numbers preclude definitive conclusions. Sorafenib acts as a substrate for UGT1A1. The phase II study did not collect direct bilirubin measurements, so whether this total bilirubin elevation is from worsening liver function caused by a toxic effect of sorafenib, a benign inhibitory effect of UGT1A1 leading to decreased bilirubin glucuronidation, or simply disease progression remains unclear. Despite a shorter course of therapy for patients with Child-Pugh B (12.9 weeks) compared with A (24.9 weeks), sorafenib was discontinued or dose-reduced at the same rates. Median time to progres-
sion for patients with Child-Pugh A was 21 weeks (95% CI, 16–25 weeks) and 13 weeks for those with Child-Pugh B (95% CI, 9–18 weeks). Overall survival for Child-Pugh A was 41 weeks (95% CI, 36.6–63.6 weeks) and 14 weeks for Child-Pugh B (95% CI, 11.6–25.7 weeks). As would be expected, results showed that patients with Child-Pugh B fared worse than those with Child-Pugh A, and experienced more frequent worsening of their cirrhosis. However, whether these results are drug-related or from natural disease progression remains unclear. More data are needed to appropriately define the safety and efficacy of sorafenib in patients with HCC and Child-Pugh B.

In a phase I study evaluating 2 different doses of sorafenib in Japanese patients with advanced HCC, no substantial differences were seen in the incidence of adverse events between the Child-Pugh A and B groups. However, geometric means of AUC_{0–12} and maximum concentration at steady state were slightly lower in patients with Child-Pugh B cirrhosis compared with Child-Pugh A. Again, patient numbers were small. One additional study evaluating sorafenib in patients with organ dysfunction helps provide some guidance on the use of sorafenib in these patients. The most commonly reported drug-limiting toxicity among patients with elevated bilirubin at baseline was further elevation of bilirubin. Suggested recommendations regarding dosing of sorafenib from this study are: 400 mg orally twice per day for bilirubin up to 1.5 times the upper limit of normal (ULN); 200 mg orally twice per day (or 400 mg orally daily) for bilirubin 1.5 to 3 times the ULN; and to avoid sorafenib for bilirubin greater than 3 times the ULN. One caveat is that this trial was conducted in patients with different types of tumors, including HCC. The origin of the underlying cirrhosis is clearly different. This area requires further study.

How Long Should Patients Continue on Therapy Given the Lack of Validated Measures to Assess Response or Efficacy?

True objective responses for sorafenib are rare. In the SHARP trial, partial responses were reported at 2%, similar to the phase II trial in which patients treated with sorafenib had a partial response rate of 2%. However, 33.6% of patients had stable disease (SD) for 16 weeks or more, and central “tumor necrosis” in response to sorafenib was frequently noted, although the significance of this finding, if any, has not been determined.

A subanalysis to evaluate the correlation between tumor necrosis and response was performed. CT scans of 12 patients (median age, 73 years; 8 men) were evaluated. Five patients had SD or SD with necrosis; 7 progressed on therapy. Median survival (from landmark analysis) was 4.8 months among responders and 3.1 months among nonresponders. The ratio between tumor necrosis and volume (N/T) was significantly associated with response, with responders having greater increases in N/T relative to baseline compared with nonresponders (P = .02). N/T was not significantly associated with overall survival. N/T as part of evaluating response must be further examined in a large clinical study. Importantly, tumor necrosis is a common result of TACE and has been described in different clinical studies evaluating targeted agents in HCC. It suggests a need for radiologic techniques other than Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate HCC response. This may be especially helpful in HCC given the complexity of the disease and its association with liver cirrhosis.

Future Direction for Systemic Therapy in Advanced HCC

Although sorafenib is now established as part of standard therapy for advanced HCC, its overall benefit is modest, and unresectable HCC remains uniformly fatal. In the advanced disease setting, a logical step is to see if combinations of sorafenib and other biologic or chemotherapeutic agents can enhance survival. Sorafenib was evaluated in combination with doxorubicin as part of a randomized, double-blinded, phase II study of doxorubicin plus sorafenib compared with doxorubicin plus placebo in patients with HCC who had not undergone any prior systemic therapy. The primary end point, median time to progression, was 9 months for the doxorubicin-plus-sorafenib arm and 5 months for the doxorubicin-plus-placebo arm. An exploratory comparison of overall survival between the arms showed a significant difference of 13.7 months favoring doxorubicin plus sorafenib versus 6.5 months for doxorubicin plus placebo (P = .0049; HR, 0.45). The toxicity profile was similar between the arms, with expected toxicities
commonly seen with single-agent doxorubicin and sorafenib. More left ventricular dysfunction occurred in the doxorubicin plus sorafenib arm in 19% of the cases (all grades), with 2% grade 3 to 4, compared with 2% all grades for the doxorubicin plus placebo arm. Synergy between doxorubicin and sorafenib may be explained by the sorafenib raf kinase inhibition, leading to upregulation of ask-1 mediated apoptosis, with the latter being induced by doxorubicin. Nonetheless, the improved median overall survival of the patients receiving the combination of doxorubicin plus sorafenib is now the basis for a larger randomized trial evaluating the combination versus sorafenib alone.

Sorafenib is also being investigated in combination with erlotinib. In a phase I trial conducted in solid tumors, fatigue and diarrhea were most commonly reported (grades 1 and 2). The diarrhea was a dose-limiting event at higher doses. Skin toxicity incidence and extent were similar to the single-agent experience of the 2 agents. A dose-dependent hypophosphatemia, typically attributed to sorafenib, was noted to be exacerbated by the combination. The study had only 1 patient with HCC whose best response was SD.

Interest in the combination probably emanates more from the impressive data reported on the use of erlotinib with another antiangiogenic agent, bevacizumab, in patients with HCC. Median progression-free survival was 9 months, and median overall survival was 15.65 months. Grade 3 and 4 fatigue was reported in 20% of cases, hypertension in 15%, and similar-grade gastrointestinal bleeds in 12.5%. The outcome of this study supports the biologic relevance of this combination of therapy in HCC, and deserves further exploring.

Other strategies of interest in the advanced HCC arena include comparison of sorafenib with other antiangiogenic agents. Contenders include a potent antiangiogenic and tyrosine kinase inhibitor, sunitinib. The data supporting sunitinib in HCC are based on 2 phase II clinical trials. In the first of these, of 26 patients with sunitinib at 37.5 mg continuous daily dosing, 10 (38.5%) showed SD, with a median progression-free survival of 4.1 months. In this particular study, dynamic contrast-enhanced MRI was performed to assess changes in tumor permeability. The mean tumor permeability (Ktrans) after 2 weeks of sunitinib therapy in 13 patients decreased from mean baseline value of 3.77 to 1.06, although the clinical relevance of this, if any, remains to be determined. The second study showed similarly promising results at the dose of 50 mg, with median time to progression of 21 weeks and median overall survival of 45 weeks.

Another need is obviously in second-line therapy, which is currently the subject of many studies evaluating novel agents.

**Potential Other Uses of Sorafenib in HCC**

The scenarios of key importance are 1) surgical adjuvant setting, 2) peri-transarterial chemoembolization of embolization, and 3) bridging therapy to transplantation.

The logical next step in the development of a drug that has shown a survival advantage in the advanced setting is to study it in the adjuvant setting. Certain biologic observations further justify this step for sorafenib. A study evaluating the tumor microvessel density (MVD) in an animal model to define angiogenic activity in tumors subjected to TAE found that tumors treated with TAE showed varying degrees of central necrosis, with residual viable tumor cells in the periphery. Animals treated with TAE had significantly higher tumor MVD than controls (23.6 vs. 17.5; \( P = .001 \)) and showed a statistically significant increase in VEGF levels compared with the control group. Considering that TAE of hepatic tumors results in the stimulation of angiogenesis in the residual viable tumor, which could have an adverse effect on the therapeutic efficacy of TAE, the use of an antiangiogenic therapy (e.g., sorafenib) seems plausible to curb that angiogenic drive. A study evaluating sorafenib in the adjuvant setting is underway. Similar efforts are also studying the use of sorafenib after TACE, with different schedules for administering the 2 modalities.

Regarding transplantation, the main interest would be to evaluate sorafenib as a bridge to transplant therapy that would maintain patients on the list and avoid dropout. Notably, this may only apply to patients with good liver function who can tolerate sorafenib and are considered transplant candidates, and the number of patients with this scenario is not necessarily extensive. Questions remain regarding safety, particularly a bleeding risk. It remains unclear how to handle the risk for bleeding in patients awaiting transplantation and maintained.
on sorafenib when an orthotopic liver suddenly becomes available.

**Conclusions**

Sorafenib is approved by the FDA for patients with unresectable HCC. Many key questions remain regarding the use of sorafenib in HCC, particularly its use in conjunction with local therapies; its role, if any, in the adjuvant setting; the question of possible inferior efficacy in hepatitis B; and its role in treating patients with Child-Pugh B and C cirrhosis. Ongoing studies will help answer some of these questions.

**References**


