What Is the Indication for Sorafenib in Hepatocellular Carcinoma? A Clinical Challenge

In this review article we will discuss the current data on, and future role of, sorafenib in the treatment of hepatocellular carcinoma beyond Child-Pugh A cirrhosis, in conjunction with local therapy, and in a transplant setting.

Hepatocellular carcinoma (HCC) in the United States accounts for approximately 23,000 new cases annually.[1] The incidence of HCC continues to increase, partly as a result of the unsolved problem of hepatitis C and deficient screening in high-risk patients. Globally, HCC is the fifth most common cancer worldwide and the third most common cause of cancer mortality.[2] The only potentially curative options for patients with HCC are liver resection, radiofrequency ablation (RFA), and liver transplantation (LT). Patients who are fortunate enough to undergo LT have a 4-year survival rate of 85% if the tumors are within the Milan criteria. Recurrence rates in this patient population range from about 8% to 12%.[3] However, among patients undergoing hepatic resection in whom the procarcinogenic liver is not replaced, the disease recurrence rate can exceed 70% at 5 years.[4] Other noncurative options include local therapies such as transarterial chemoembolization (TACE), radioembolization, RFA, and systemic therapy.[5] Advanced HCC carries a very poor prognosis, and use of cytotoxic agents has provided only marginal benefit.[6,7]

In 2007, sorafenib was approved in United States and Europe for advanced HCC based on results from the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial.[8] Sorafenib is an oral multikinase inhibitor that blocks tumor cell proliferation by targeting multiple pathways including the Raf/mitogen-activated protein kinase/extracellular signal–regulated kinase (Raf/MEK/ERK) signaling pathway, along with tyrosine kinases (TKs), VEGF receptor 2 (VEGFR-2), VEGFR-3, and the platelet-derived growth factor receptor β (PDGFR-β) pathway.[9] In the landmark SHARP trial, 602 patients with advanced HCC were randomized to either sorafenib at 400 mg twice a day or to placebo.[8] The final result showed that sorafenib had overall survival (OS) and time to tumor progression (TTP) benefits in patients with advanced HCC, compared with placebo. Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group. In Asia, a similar phase III trial was being conducted simultaneously. This trial also showed a similar magnitude of benefit in the sorafenib arm compared with the placebo arm.[8,10] Based on these two phase III trials, sorafenib became the first molecularly targeted therapy to show an OS benefit, establishing it as the first new standard treatment for advanced HCC.

The new data are now being met with cautious optimism, but there are several unanswered questions. The US Food and Drug Administration (FDA) authorized use of sorafenib for patients with “unresectable hepatocellular carcinoma,” a very vague and broad indication. In Europe, the indication is even broader, as sorafenib is indicated for “hepatocellular carcinoma.” Therefore, the exact indication for sorafenib in advanced HCC is confusing and gives rise to many uncertainties, including use of sorafenib in patients with decompensated liver disease, use in conjunction with local therapy, or use in a transplant setting. Most of the patients enrolled in these large phase III trials had well-compensated liver function (Child-Pugh A cirrhosis); therefore the utility of sorafenib in Child-Pugh class B or C cirrhotic patients remains unknown. Also unclear is the potential role of sorafenib in combination with locoregional therapies, as well as its potential use in liver-transplant settings. The safety and feasibility of the implementation of sorafenib as a pretransplant neoadjuvant agent, or as an adjuvant therapy for posttransplant HCC recurrence, are uncertain. These practical questions have to be addressed as we deal with a complex disease in which an oncologic state evolves from conditions of liver dysfunction or immunosuppression. In this review article we will discuss the current data on, and future role of, sorafenib in the treatment of HCC beyond Child-Pugh A cirrhosis, in conjunction with local therapy, and in a transplant setting. The role of sorafenib in combination with other targeted therapies or
other promising agents in the treatment of advanced HCC is beyond the scope of this article and will not be discussed.

**Sorafenib in Child-Pugh B or C Cirrhosis**

The safety and efficacy of sorafenib have been proven in patients with Child-Pugh A cirrhosis based on the aforementioned two large phase III trials. Little is known about the safety and efficacy of sorafenib in patients with Child-Pugh class B or C cirrhosis. Nevertheless, since there are no other effective treatments for cirrhotic patients with advanced disease, many single institutions have used sorafenib in these patients.

Prior to the SHARP study, a phase II trial by Abou-Alfa et al analyzed use of sorafenib in both Child-Pugh A and B cirrhotic patients. In this trial, out of 137 patients, 38 had Child-Pugh B cirrhosis and 99 had Child-Pugh A cirrhosis. In the analysis of the study, toxicity profiles for Child-Pugh A and B cirrhosis, drug discontinuation rates, and dose reduction rates were similar in both groups. Nevertheless, overall outcome was much worse in the Child-Pugh B group, with an overall survival (OS) outcome of 3.5 months and time to tumor progression (TTP) of 3.3 months.

Another large retrospective study from the Western Hemisphere, by Pinter et al, included 23 patients with Child-Pugh B cirrhosis and 10 with Child-Pugh-C cirrhosis. Results revealed an OS of 4.3 months and a TTP of 2.9 months in the Child-Pugh B group, similar to findings from the phase II trial by Abou-Alfa et al. In the Child-Pugh C group, however, OS was only 1.5 months, and the authors concluded that sorafenib should not be used in patients with advanced-stage cirrhosis.

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<th>Table 1</th>
<th>Efficacy of Sorafenib by Child-Pugh Class</th>
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<td>Two of the largest Asian experiences in patients with Child-Pugh B cirrhosis are described in studies from Korea, where hepatitis B is the number one risk factor for HCC. Lee et al reported on 29 patients with Child-Pugh B cirrhosis who received sorafenib and exhibited an OS of 3.7 months. Another series included 23 patients with Child-Pugh B cirrhosis; TTP was 2 months but OS was not reported. Results of other small series that included patients with Child-Pugh B cirrhosis are listed in Table 1. In terms of drug-related toxicity profiles, most of these retrospective analyses did not distinguish between Child-Pugh A and B cirrhosis. Four of the studies did attempt to make a distinction, however, and the toxicities are outlined in Table 2.</td>
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<th>Table 2</th>
<th>Toxicities of Sorafenib According to Child-Pugh Class</th>
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<td>There are data showing no statistically significant difference in the pharmacokinetics (PK) of sorafenib in Child-Pugh A versus Child-Pugh B patients. A phase I trial conducted in Japan also showed no substantial differences in the incidence of adverse events or clinically relevant differences in PK between the Child-Pugh A and B groups. Overall, toxicity profiles for Child-Pugh B patients seem to be similar to or slightly worse than those for Child-Pugh A patients. However, toxicity reflecting worsening hepatic dysfunction, such as hyperbilirubinemia, encephalopathy, and ascites, appears to be to be greater in Child-Pugh B patients. Notably, worsening bilirubin levels were reported in 40% of Child-Pugh B patients, compared with 18% of Child-Pugh A patients. Nevertheless, because direct bilirubin levels were not reported, it is unclear if the rise in total bilirubin was related to sorafenib as a result of decreased bilirubin</td>
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Sorafenib Plus Local Therapy

There is a good rationale for using sorafenib in conjunction with local therapy such as transarterial chemoembolization (TACE) or radioembolization. A study from China showed that TACE before hepatic resection enhances angiogenesis in HCC cells by upregulating the expression of vascular endothelial growth factor (VEGF).[23] Importantly, however, it has been shown that after the TACE procedure there is a rise in serum VEGF levels, which can feed the residual cancerous tissue and allow tumor cell proliferation.[24] Because of this, it might be beneficial to add an antiangiogenic agent to repress tumor angiogenesis after the patient has received therapies to induce tissue ischemia, such as TACE. Another potential advantage of these combinations is that use of an antiangiogenic systemic agent might enable control of systemic tumor cell spread. In the SHARP study, about 50% of patients did receive some form of local therapy prior to treatment with sorafenib.[8]

Efficacy of sorafenib in Child-Pugh B patients in the small series reported in the medical literature seems to be very modest, with OS ranging from 2–5 months. Difficulty in evaluating survival in Child-Pugh B patients has to do with the coexistence of HCC and advanced-stage liver disease. Patients who have Child-Pugh B cirrhosis without HCC have a 1-year survival rate of about 80%.[20] Therefore, deaths from cirrhosis could potentially mask treatment-related antitumor efficacy. The potential for a clinically meaningful gain in OS with use of sorafenib in Child-Pugh B patients can only be evaluated in a prospective, randomized, placebo-controlled trial. However, placebo-controlled trials in Child-Pugh B patients will be very difficult in an era in which drug regulatory agencies allow sorafenib to be used to treat patients with HCC and any degree of liver failure.

These retrospective analyses, therefore, give us important insights into use of sorafenib in Child-Pugh B patients, despite their obvious limitations. It is hoped that, as more institutions publish their experiences with incorporating sorafenib into the treatment of patients with advanced cirrhosis, we will gain further knowledge about its efficacy and toxicity profiles in a variety of patient settings. In the future, instead of lumping all Child-Pugh B cirrhosis patients together in the outcomes analysis, we should consider categorizing them into subgroups. For example, Child-Pugh B patients with a Child-Pugh score of 7 may have a better outcome with sorafenib than those with a score of 8 or 9. Unfortunately, HCC patients who are classified as having Child-Pugh C disease will most likely not benefit from any therapeutic options except for LT secondary to liver cirrhosis. Quality of life also should be part of the assessment, given that OS in most patients with HCC and Child-Pugh C disease is measured in months.

GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and Of its Treatment with Sorafenib) is an ongoing global, prospective, noninterventional study of patients with unresectable HCC and for whom the decision has been taken to treat with sorafenib under real-life practice conditions.[21] The purpose of this study is to evaluate the safety and efficacy of sorafenib in different subgroups, especially in patients with Child-Pugh B disease, or in conjunction with local therapy, a treatment option for which data are limited. The plan is to accrue more than 3,000 patients, and the findings are likely to provide us with valuable information about certain HCC patient subgroups.

Meanwhile, until more definitive data become available, it is imperative that clinicians employ caution and their best judgment when using sorafenib in patients with Child-Pugh B cirrhosis. As expected, patients with Child-Pugh C cirrhosis had a very poor outcome despite being on sorafenib, with median survival times between 2 and 3 months.[13,22] The poor outcome is most likely related to underlying liver cirrhosis, so it is highly unlikely that sorafenib or any other therapy will provide those patients with clinically meaningful benefits. Biomarker development or new information about tumor characteristics that identify subgroups of patients who may respond to sorafenib independent of Child-Pugh stage may be helpful in the future.
TACE is the most common local therapy used in patients with HCC. Transarterial radioembolization has been implemented in recent years, and even more recently, drug-eluting beads loaded with doxorubicin (Adriamycin) have been used. TACE involves the injection of chemotherapeutic agents into the artery feeding the tumor, using lipiodol (Ethiodol) as a carrier. It is traditionally used for treatment of large unresectable HCCs that are not eligible for other treatments such as resection, RFA, or liver transplantation. Although data on TACE are controversial, there are two randomized controlled trials and a meta-analysis that support use of TACE in patients with advanced HCC.[25-27] Drug-eluting beads loaded with doxorubicin have an advantage over standard TACE in that they can deliver higher levels of chemotherapy released to the target over time, thereby decreasing potential systemic side effects. A recent randomized phase II trial comparing conventional TACE versus drug-eluting-bead (DEB) embolization showed that DEB embolization was associated with better response and better patient tolerance than standard TACE.[28]

Another local mode of therapy that is gaining popularity is radioembolization using intrahepatic arterial administration of yttrium 90 (Y90)-tagged glass (TheraSphere) or resin (SIR-Spheres) microspheres. Because HCC is a hypervascular tumor, microspheres injected intraarterially will preferentially deliver to the tumor-bearing area and selectively emit high energy, high-penetrating-power radiation to the tumor. One of the advantages of radioembolization is that it can be used safely in patients with portal vein thrombosis, because it is less embolic and spares the arterial blood flow to the treated liver parenchyma. While multiple trials show that radioembolization has some antitumor activity, there are no prospective data showing improved survival benefits compared with placebo or TACE.[29,30]

**Table 3** provides currently available information about the combination of sorafenib with local therapy. As one can see, most of the trials are small retrospective or prospective studies in only abstract forms, with the exception of one phase III trial. This trial was presented at the 2010 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology.[31] Investigators randomized patients with advanced HCC to TACE alone versus TACE plus sorafenib. In this trial, sorafenib was started a mean of 9.1 weeks after TACE. The primary endpoint was TTP. Despite the sound rationale for administering combination therapy, the trial did not meet its primary endpoint. There were several study limitations, however: Most patients only received one course of TACE despite the fact that most had bilobar disease; the rationale for this is unclear. The duration of treatment with sorafenib was relatively short, with a high rate of discontinuation (45%) secondary to adverse events. Inclusion criteria in this study were very heterogeneous, with patients having fewer than 3 lesions or up to 10 lesions. In addition, definitions of complete response and progression were unclear in the study. It is hoped that the investigators will answer some of these questions in the published manuscript.

Combination of radioembolization using Y-90 SIR-Spheres or DEB embolization and sorafenib also has been studied (see Table 3). The largest series using radioembolization with sorafenib was done in Asia.[32] The trial included 35 patients with Barcelona Clinic Liver Cancer (BCLC) stage B and C disease. Results were a cause for optimism, with 33% of patients achieving a complete or partial response. The combination was well tolerated, as there were only three treatment-related adverse events of grade 3 and above reported. The largest series assessing combination of sorafenib with DEB was presented by a group from Johns Hopkins.[33] Preliminary analysis reveals that the combination appears to be safe, as it did not result in any greater toxicities than were seen with either therapy alone. The outcomes of this trial have not been reported.

In conclusion, trials evaluating local therapy with and without sorafenib are very small and too premature. Most have been communicated only in the form of study abstracts, leaving many questions unanswered. Primary endpoints and response criteria were not well defined in most of these studies. Because of these factors, no robust conclusion can be drawn in regard to the combined therapies investigated thus far. The critical question that needs to be answered is whether the addition of sorafenib to local therapy induces a better outcome than local therapy alone. Okita et al attempted to answer this question in a phase III trial,[31] but failed to do so because of several limitations.
There are other lingering questions as well. For example, when should we initiate treatment with sorafenib? Maybe it makes sense to start sorafenib prior to TACE in order to block upregulation of VEGF in the tumor as well as in serum. Should we stop sorafenib 1 to 2 days prior to initiating local therapy, given the concerns about toxicity? As one can see in Table 3, the schedule of sorafenib administration is different in each trial. Another major problem is the lack of consistency regarding the frequency of scheduling TACE procedures and the type of chemotherapy agent or embolic material used. In the past, TACE has been given as frequently as two courses per month, but under this schedule it has induced hepatic decompensation in 7.5% of patients.[26,34] Clearly, the toxicity profile needs to be closely looked at with these combinations. Large phase II and III studies underway are using a combination of local therapy plus sorafenib; the outcomes of these trials are eagerly awaited. It is hoped that, as these data become more mature and as these studies are developed into full manuscripts, we will have better insights into these trials. In oncology, we have learned from the past that one plus one does not always equal two, and sometimes can equal zero. Therefore, careful consideration must be given prior to combining sorafenib with local therapy in patients with HCC.

Sorafenib and Liver Transplantation

The neoadjuvant setting

If disease is caught at an early stage, then LT is a potential curative option. However, the shortage of donor organs leaves waitlisted patients at risk for disease progression beyond transplant criteria. Prevention of waitlist dropout has fueled investigation into a wide array of locoregional therapies as “bridging therapy” or neoadjuvant therapy prior to LT. The purpose of these therapies would be to decrease the dropout rate, to prevent tumor progression, and possibly to increase overall survival. Currently most of the transplant institutions are implementing some form of neoadjuvant therapy despite the lack of randomized prospective data.[35] Sorafenib potentially can be used as a neoadjuvant therapy in patients awaiting LT, since the drug can extend the time to disease progression. Another possible use of sorafenib would be in patients who are not candidates for local therapy secondary to elevated bilirubin levels. There is a phase I trial showing that sorafenib can be used in patients with bilirubin levels > 1.5 times but < 3 times the upper limit of normal (ULN) with dose reduction.[36] Using sorafenib in patients with bilirubin levels > 3 times the ULN may be problematic, however, as patients in the phase I trial could not even tolerate a dosage of 200 mg every other day.

One analysis by Vitale et al, using the Markov model, showed that sorafenib given as neoadjuvant therapy can be cost-effective in comparison with no therapy for Milan criteria HCC patients waiting for LT, particularly for median times to LT that are < 6 months.[37] There is concern associated with the use of sorafenib in pretransplant patients, however. Because sorafenib is a VEGF inhibitor, there is an associated risk of bleeding and/or wound healing complications. Bevacizumab (Avastin), a monoclonal antibody to VEGF, has been used as neoadjuvant therapy prior to liver resection for advanced colorectal cancer.[38] Yet the antiangiogenic effects of bevacizumab, coupled with its long half-life (approximately 21 days), have led to concern that preoperative bevacizumab may affect liver regeneration and wound healing, requiring a waiting period of at least 6 weeks after the last dose of bevacizumab before performing surgical resection.[38-40] Sorafenib has an advantage over bevacizumab in that it has a much shorter half-life, but safety data prior to surgery are sorely lacking. The only prospective data that we have are in renal cell carcinoma patients who received sorafenib prior to nephrectomy; sorafenib was held at 24-48 hours prior to surgery, and no surgical complications were seen.[41] In a transplant setting, waiting 24 hours after sorafenib intake is not feasible, as a donor liver can become available at any time.

Therefore, the treatment safety profile is of the utmost importance. Currently there are no prospective trials reported, but several case reports have been published in which sorafenib has been used as a neoadjuvant agent in the pretransplant setting.[42,43] In those small case reports, there were no unforeseen surgical complications. Currently there is a small pilot study ongoing at the Cleveland Clinic to investigate the safety and feasibility of using sorafenib in HCC pretransplant patients.

The adjuvant setting

Patients whose HCC falls within the Milan criteria and who undergo LT tend to have a favorable
outcome, but patients with high-risk tumor features (HCC beyond the Milan criteria, poorly differentiated tumors, presence of microvascular spread or satellite lesions) have a significantly higher rate of posttransplant tumor relapse. Naturally, therefore, it will make sense to conduct a trial using an effective systemic agent in an adjuvant setting to prevent tumor recurrences. An ongoing multicenter international trial (STORM: Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) is evaluating the efficacy of sorafenib in preventing tumor recurrence after liver resection or RFA. This trial does not include transplant patients, however, owing to safety concerns associated with the interaction with immunosuppressive agents. There is an ongoing pilot study assessing the safety of sorafenib as an adjuvant therapy in patients with high-risk features of recurrence after LT. The main concern would be the short-term and long-term toxicities associated with the use of sorafenib in immunosuppressed patients.

**TABLE 4**

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<th>Outcome of Sorafenib for Tumor Recurrences After Orthotopic Liver Transplant (OLT)</th>
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**Sorafenib for post-transplant recurrent HCC**

Another area of interest is the use of sorafenib in patients with recurrence of HCC after LT. Currently no standard therapy is available for these patients. In the large phase III SHARP and Asia Pacific trials, patients who experienced a recurrence after transplant were excluded. The use of this drug in recurrent HCC after LT has therefore never been studied prospectively. Similar to the adjuvant setting after LT, a concern in transplant patients with recurrent HCC is the potential interaction between immunosuppressive medications and sorafenib. Even though there are no prospective trials in this setting, many institutions have reported their experience with the use of sorafenib in posttransplant patients who have tumor recurrences. Table 4 describes those findings. So far, only a few published reports exist, with little detailed information. In terms of its safety profile, however, it definitely seems feasible to use sorafenib concomitantly with immunosuppressive medications. The largest series, which have been published by investigators from Korea, the University of Miami, and the Cleveland Clinic, show that toxicities of sorafenib were quite manageable with dose reduction. The main difference was that the data from Korea only included patients who had HCC recurrence after living donor transplantation; this reflects a difference in the practice pattern in Korea, as most of the transplants in the United States are from cadaveric livers. Overall results seem to be promising, but based on the small sample sizes of these studies, conclusions cannot be made regarding efficacy in this setting. It would be ideal, then, to conduct a randomized prospective trial to determine the efficacy of sorafenib versus placebo in patients who have disease recurrence after LT, since there is no standard therapy.

**REFERENCE GUIDE**

- Bevacizumab (Avastin)
- Doxorubicin (Adriamycin)
- Lipiodol (Ethiodol)
- microspheres (SIR-Spheres)
For a variety of reasons, however, it will be difficult to conduct a randomized prospective trial of sorafenib against placebo. First, the number of recurrences after transplant is quite small compared with advanced HCC patients in the pretransplant setting; thus, a much longer time would be required for the trial to accrue patients, which might not be feasible. Second, there is the issue of randomizing patients to a placebo arm when sorafenib is already available in the market. To begin, it would be reasonable to conduct a phase I trial to find out the correct dose of sorafenib to use in this setting, since most of the retrospective studies have required dose reduction secondary to toxicity. Then, a small phase II trial could be conducted with a single arm of sorafenib and comparing OS data against historical data, or a randomized phase II study could compare sorafenib against placebo, with patients on the placebo arm allowed to cross over upon progression. These trials would still require collaboration from many institutions in order to accrue in a timely fashion, and PK studies would be helpful as well.

**Conclusion**

In summary, the approval of sorafenib marks a major advance in the treatment of advanced HCC. Even though the indication for sorafenib is for patients with unresectable HCC, the published data and clinical experience thus far do not provide definitive conclusions about the use of sorafenib in advanced HCC patients with cirrhosis beyond Child-Pugh A classification. Most of the data reviewed in this article were from small-scale prospective or retrospective studies, resulting in a low level of evidence.

It is important that clinicians continue to exercise caution and their best judgment when treating patients with HCC beyond Child-Pugh A, until more definitive data become available. Ideally we would like to have prospective data for each Child-Pugh classification. While there are ongoing prospective trials—for example, those investigating sorafenib in combination with local regional treatment, as previously noted—for various reasons there are certain circumstances in which prospective trials will not be conducted. Indeed, there are many limitations to the current retrospective data, including lack of randomization to specific treatment arms and the lack of a placebo-control arm. These factors limit robust evaluation of the efficacy of any treatments received by these patients. Despite the limitations of retrospectively designed studies, information from retrospective/single-institution studies provides us with important insights to aid in decision-making when treating patients with end-stage liver disease complicated by HCC. In the future, as more retrospective and prospective data become available, we will be able to determine the best treatment options in a variety of settings and stages of liver disease, in order to maximize the outcome and benefits for our patients.

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