HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

The Role of Sorafenib in Hepatocellular Carcinoma

Pierre Gholam, MD
Associate Professor of Medicine
Case Western Reserve University School of Medicine
Medical Director, Liver Center of Excellence
University Hospitals Case Medical Center
Cleveland, Ohio

G&H Which patients with hepatocellular carcinoma benefit from sorafenib therapy?

PG Patients who have unresectable hepatocellular carcinoma (HCC), defined as a tumor that the surgeon is unable to resect owing to medical, surgical, or psychosocial contraindications, are potential candidates for sorafenib (Nexavar, Bayer/Onyx) therapy. These patients typically have disease beyond a localized small lesion, which is usually defined as a T2 lesion. They often have fairly advanced disease, including macrovascular invasion and extrahepatic spread, but they typically do not have very impaired liver function, as evidenced by having Child-Pugh C cirrhosis. Therefore, a fairly wide group of patients can potentially benefit from sorafenib therapy.

Other patients who may benefit from sorafenib therapy include those who have relatively early disease but are not candidates for liver transplantation, ablation, or resection.

G&H What were the findings of the AP and SHARP trials?

PG The AP (Asia-Pacific) and SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trials were 2 large, randomized, placebo-controlled trials that were conducted in the Asia-Pacific region and in Europe and the United States, respectively, to determine whether sorafenib was an effective first-line treatment for patients with unresectable HCC. These double-blind trials randomly assigned patients to either sorafenib or placebo. Approximately 30% of patients had received prior treatment in the form of local-regional therapy, and a large percentage of them had extrahepatic spread of cancer or macrovascular invasion. The primary endpoint in both trials was survival, and additional endpoints included time to radiologic progression and time to symptomatic progression.

Both trials reported improved survival in the sorafenib group over the placebo group, confirming the primary endpoint. In fact, the SHARP study was stopped early based on evidence that the sorafenib arm had increased survival at the time of interim analysis. The results of the SHARP trial led to the approval of sorafenib by the US Food and Drug Administration for the treatment of HCC, and this agent is currently the only systemic therapy approved for this disease. Another interesting endpoint was the almost doubling of the time to radiologic progression in the SHARP trial.

The patients who were enrolled in the AP trial experienced more adverse events in general. The reason for this was not entirely clear, although one possibility was that these patients tended to have more advanced disease and, therefore, were potentially more susceptible to adverse events in general. However, the efficacy of sorafenib was essentially equivalent in both trials.

G&H Does sorafenib have a role in combination therapy for HCC?

PG There have been a number of single-center and multicenter trials looking at combination therapy of sorafenib with various interventions, including transarterial

chemoembolization and radioembolization. Several studies have also looked at sorafenib with other chemotherapeutic agents, including bevacizumab (Avastin, Genentech). The overall assessment of these studies is that they unfortunately have had significant problems with study design or conduct.

One example is the SPACE (Sorafenib or Placebo in Combination With Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma) trial, which was a large multicenter study that examined whether the combination of sorafenib and transarterial chemoembolization improved survival compared with sorafenib alone. This trial had significant heterogeneity in the way that transarterial chemoembolization procedures were performed, as well as in the frequency of these procedures and the intervals between them. This resulted in a data set that was somewhat difficult to interpret. The final conclusion was that the addition of sorafenib in the study population did not seem to increase survival. Combination treatment did, however, lead to an increase in time to radiologic progression and was safe and well tolerated compared with transarterial chemoembolization alone.

Likewise, the data available thus far do not support the combination of 2 chemotherapeutic agents to treat unresectable HCC. Nevertheless, I think that further investigation is required to definitively determine the benefit of combination therapy or the lack thereof. Several interesting studies on this topic will be reporting results soon, including a study on the combination of sorafenib and yttrium-90 radioembolization. The primary endpoint of this international, multicenter study, which is called STOP-HCC (Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer), is overall survival. The results are eagerly awaited.

G&H Can sorafenib be effectively dose reduced if necessary?

PG The impact of dose reduction has not been explored in great detail in the setting of sorafenib randomized clinical trials. However, we do have some observational data from the GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment With Sorafenib) registry, which is the largest known registry of patients taking sorafenib in a phase 4 observational setting. Based on GIDEON data, it appears that dose modification is quite common in real life, and there does not appear to be a dramatic change in the efficacy of the drug when patients receive lower doses over the course of therapy, such as a reduction from 800 to 400 mg daily. There also does not appear to be a significant prescriber trend toward re-escalating the dose of sorafenib once the underlying cause of the dose reduction, usually a significant adverse event, is addressed.

Therefore, it is somewhat unclear whether dose reduction by itself reduces the efficacy of sorafenib or whether patients can take a lower dose and achieve the same therapeutic benefit as with the full 800 mg per day dose. I think that the practical standard for now is to dose-reduce patients as appropriate to address adverse events in a timely manner and attempt to re-escalate the dose if the adverse event is addressed fully and effectively.

G&H Are there any difficulties with dose re-escalation?

PG Dose re-escalation is an issue that has not received much focus in sorafenib-treated patients. One of the problems with re-escalation is that it occurs in the context of a patient who has had his or her dose reduced because of a significant adverse event, usually a hand-foot skin reaction. We know that if a physician reduces the dose of sorafenib, treats the hand-foot skin reaction effectively, and then re-escalates the dose—or if the physician completely stops sorafenib therapy, re-introduces the drug at a lower dose, and then gradually increases the dose as tolerated—many patients will tolerate treatment quite well.

However, there is often both patient and physician reluctance to do this, and it is an option that prescribers should probably try to pursue more aggressively. After all, the majority of the benefits generated in the AP and SHARP trials were with the full 400 mg twice a day dose; therefore, we should try to come close to that dose in clinical practice.

G&H What are the most common adverse events associated with this drug?

PG The most common adverse events associated with sorafenib are hand-foot skin reactions, diarrhea, and fatigue. Other adverse events include asymptomatic hypophosphatemia or hyperamylasemia. Patients also may experience adverse events commonly associated with liver disease, such as elevation of liver enzymes and cytopenias. Some of these adverse events may be a byproduct of treatment, but most of them are related to underlying liver disease.

G&H How are these adverse events usually managed?

PG Hand-foot skin reactions, which generally occur in the first 4 weeks of therapy, are managed according to a detailed symptom-driven algorithm. Depending on the grade of the reaction, the patient may continue with sorafenib therapy while starting treatment for the reaction, which would usually include the application of a high-concentration urea cream, avoidance of repetitive movements and temperature extremes, and waiting to

see whether these interventions help the condition. The preferred approach for managing up to a grade 1 skin reaction is to avoid dose reduction, but this is usually necessary for grade 2 reactions.

For patients with a grade 3 or greater hand-foot skin reaction, it is usually necessary to hold sorafenib, in addition to implementing all of the interventions mentioned earlier. The physician could certainly rechallenge patients who develop grade 3 reactions with sorafenib because many of them will be able to continue therapy without recurrence of the same adverse events.

G&H Should patients be monitored for hypophosphatemia?

PG Although hypophosphatemia has been reported in 35% of sorafenib patients (vs 11% of placebo patients), I do not routinely treat hypophosphatemia or monitor patients for it in the setting of sorafenib therapy. I am, however, aware that some providers do monitor the phosphate level and treat it if low owing to muscle risk and cardiomyopathy as well as fatigue.

G&H What are the usual next steps if sorafenib therapy is not effective?

PG If patients experience progression of disease and no longer appear to derive clinical benefit from sorafenib therapy, then other options could be considered, including, if appropriate, local-regional therapy with transarterial chemoembolization or radioembolization. In certain situations, clinical trials for second-line agents would be reasonable to consider; I have referred patients whose disease has failed to respond to sorafenib to such trials. In addition, the CyberKnife Robotic Radiosurgery System (Accuray Incorporated), which is a stereotactic body radiation therapy, can be applied to lesions when allowed by the patient's overall status and tumor location.

G&H What are the next steps of research in this area?

PG We are still waiting for more data regarding combination therapy with sorafenib and either a local-regional intervention or another chemotherapeutic agent. There are several interesting ongoing studies on combination therapy with sorafenib, for example, the previously mentioned STOP-HCC study.

There are also a number of other systemic agents that are currently being tested, including agents that work through other mechanisms. Some of these agents may have a component of angiogenesis, while others may work through pro-oncogenic pathways. For example, lenvatinib (Lenvima, Eisai) is currently undergoing a phase 3 study in which it is being tested as first-line therapy compared with sorafenib. Results from many of these studies should be released in the next 6 months, at which time we will hopefully have clarity as to whether additional options are available aside from sorafenib.

Dr Gholam has received honoraria from Bayer/Onyx for speaking, consulting, and being on advisory boards. He has also received research support from Bayer/Onyx.

Suggested Reading

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