

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Current Status of Sorafenib Use for Treatment of Hepatocellular Carcinoma



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G&H What is the current understanding of the mechanism of action of sorafenib?

HE-S Sorafenib (Nexavar, Bayer) is an orally administered, molecularly targeted medication for the treatment of hepatocellular carcinoma (HCC). This multikinase inhibitor exhibits activity against the RAS/RAF kinases and affects cell proliferation and angiogenesis.

G&H Currently, in which HCC patients is sorafenib indicated?

HE-S According to the most recent guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, the current place of sorafenib is in patients with advanced HCC that is not amenable to curative treatments such as transplant or resection. Specifically, sorafenib is the standard systemic therapy in patients with well-preserved liver function (Child-Turcotte-Pugh [CTP] class A), as well as in carefully selected patients with CTP class B with advanced tumors (Barcelona Clinic Liver Cancer stage C or D) or tumors that have progressed after locoregional therapy.

G&H What is the latest research in terms of the effectiveness of sorafenib monotherapy in patients with HCC?

HE-S Approval of sorafenib by the US Food and Drug Administration (FDA) came as a result of large,

multicenter, randomized, controlled studies: the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial and the AP (Asia-Pacific) trial. Both of these trials were conducted using sorafenib vs placebo, and both showed a significant but modest increase in overall observed survival with the use of sorafenib.

Thus, the question then became whether the efficacy results shown in these 2 randomized, controlled trials could be replicated in effectiveness data from community practice. Some of these data come from the large GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment With Sorafenib) registry, which contains real-life observations of sorafenib treatment for HCC. By and large, this registry shows gains in overall survival with the use of sorafenib in community practice similar to the gains obtained in randomized trials of the drug. Additional data show similar effectiveness in elderly patients (enrolled in Medicare), who were not highly represented in the clinical trials for FDA approval.

Finally, although the FDA clinical trials were limited to patients with CTP class A, effectiveness data are present for CTP class B using secondary analyses from clinical trials. Overall, the median survival in CTP class B is shorter compared to CTP class A counterparts (eg, 4-5 months vs 10-13 months, respectively), but there is a similar incidence of adverse events.

G&H Could you further discuss recent research on the use of sorafenib in other HCC stages?

HE-S There have been several comparative (ie, retrospective) studies, as well as data from the GIDEON registry in a preplanned analysis, showing that the survival benefit observed among patients who received sorafenib seemed not to be different between patients with CTP class A and patients with CTP class B. However, due to the observational nature and limited scope of the available data, further evidence is required, either from additional prospective observational data or from a clinical trial. Such data may come from prospective studies such as BOOST (Sorafenib in First-Line Treatment of Advanced B Child Hepatocellular Carcinoma; ClinicalTrials.gov Identifier: NCT01405573), which is currently examining the use of sorafenib in patients with CTP class B.

G&H Have there been any other important observations from real-world experiences or registries?

HE-S Population-based US data are available from the SEER (Surveillance, Epidemiology, and End Results)-Medicare database, which consists of patients who are generally 65 years and older and have Medicare coverage. According to an analysis of the SEER-Medicare database by Parikh and colleagues, patients who received sorafenib had a median survival of 150.5 days compared to only 62 days for controls. It appears that real-world effectiveness of sorafenib is consistent and can be replicated.

Therefore, according to the clinical trials for FDA approval and the aforementioned observational data, the drug works well in a subset of patients with HCC and, thus, should be considered in the appropriate setting.

G&H What are the most recent cost-effectiveness data regarding sorafenib treatment?

HE-S There have been several formal cost-effectiveness studies performed suggesting that sorafenib treatment may be cost-effective for patients with CTP class A. However, real-world data on this issue are still required before it can be definitively determined whether expanding sorafenib to other subgroups of patients is cost-effective. For example, simulation studies in Europe have shown that dose-adjusted sorafenib in daily practice is cost-effective; however, using US SEER-Medicare data, sorafenib was not cost-effective.

G&H What is the most recent research on the drug's effect on quality of life?

HE-S The quality of life of patients with advanced liver disease and HCC is generally low, particularly in the

stages in which sorafenib is used. Ongoing research shows at least no diminution of quality of life, and possibly some modest improvement, with sorafenib compared to no treatment. For example, a study by Shomura and colleagues of 54 patients with advanced HCC on sorafenib found that health-related quality of life was not significantly impaired in those patients who were able to complete a 1-year course of sorafenib treatment.

However, sorafenib has been associated with several side effects, most notably diarrhea, fatigue, and hand-foot-and-mouth disease, and affected patients will experience deterioration of quality of life. Fortunately, reducing the dose has been associated with amelioration of some of these side effects, and discontinuation may not be required in all patients who display side effects. Depending on the patient's response, the dose may eventually be escalated. Interestingly, it has been described that patients who develop side effects seem to have improved survival compared to those who do not.

G&H What follow-up care is needed in patients taking sorafenib?

HE-S Routine care should include proactively searching for possible adverse events; paying attention to the underlying severity of liver disease; treating decompensation of hepatic disease when it arises; considering the reduction or stopping of medication when adverse events or decompensation occurs; and then monitoring the overall response to treatment using cross-sectional imaging, looking for signs of nonprogression, progression, or regression, and gauging the continuation of treatment accordingly.

Currently, there is also a rescue therapy available, regorafenib (Stivarga, Bayer), which has shown improvement in survival among patients who progressed while on sorafenib therapy. The possibility of utilizing a second-line therapy gives further importance to follow-up regarding tumor size and progression.

G&H What is the latest research on sorafenib combination therapy?

HE-S Given the success of sorafenib and its position as the first FDA-approved chemotherapeutic agent to be used in HCC, it was logical to try to combine it with potential curative or palliative therapies for HCC. The use of sorafenib has been tested as an adjunct to surgical resection, ablation, and transarterial chemoembolization. However, in none of these settings did the combinations appear to add a significant improvement in survival. Nevertheless, there is still ongoing research on several combinations, particularly with transarterial chemoembolization.

G&H What future research is needed to improve sorafenib treatment?

HE-S It is important to identify subsets of patients with intermediate or advanced HCC who might have better response to sorafenib. This would limit adverse events and expense related to treatment in patients not as likely to experience benefit, and would enable providers to focus on the subset of patients who would benefit with perhaps a higher dose, longer duration of therapy, or more-intensified follow-up care. There are anecdotal observations of patients who have a dramatic response to sorafenib with shrinkage of tumor size and lowering of α -fetoprotein levels, so molecularly targeted studies are needed to identify these subsets of patients.

Also important is testing sorafenib in patients who have HCC due to “new” causes of liver disease, such as after the cure of hepatitis C virus infection, well-suppressed hepatitis B virus infection, or nonalcoholic fatty liver disease. These are emerging risk factors that are likely to be common in the near future, but were not represented adequately in the clinical trials.

Dr El-Serag has received research group funding from Wako, Merck, and Gilead.

(Continued from page 611)

G&H What are the priorities of research in this field?

OP The first step is to finalize the European studies and publish the results. The next step is to confirm the results with studies from other centers, including in the United States. It is always beneficial to conduct prospective, randomized trials comparing hybrid APC with other ablation therapies, such as radiofrequency ablation. As far as I know, there is 1 ongoing study in the United Kingdom that has compared the 2 therapies in a prospective, randomized trial, but more are needed.

Dr Pech has received speaker honorarium from Boston Scientific, Olympus, Fujifilm, Medtronic, Norgine, and AbbVie.

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