

Sorafenib in advanced HCC

Multikinase inhibitor is the first agent to show a survival benefit as first-line therapy in patients with inoperable disease

What's new, what's important

Systemic treatment options for metastatic hepatocellular carcinoma (HCC) are limited. All patients with HCC should be considered for a clinical trial. The US Food and Drug Administration (FDA) designation of sorafenib (Nexavar) as an orphan drug for the treatment of HCC is very promising and FDA approval of sorafenib for HCC is expected soon.

Sorafenib is an oral multikinase inhibitor that targets serine/threonine and receptor tyrosine kinases to decrease tumor growth and inhibit angiogenesis. The dose of sorafenib for HCC is 400 mg orally twice a day. The most common side effects are rash, diarrhea, fatigue, and hand-foot syndrome.

Studies combining sorafenib with cytotoxic agents and other biologic agents in HCC are ongoing.

— Jame Abraham, MD

Sorafenib (Nexavar) was recently granted fast-track status in the setting of hepatocellular carcinoma (HCC). The agent currently is approved for treatment of renal cell carcinoma. As reported at the 2007 Annual Meeting of the American Society of Clinical Oncology,¹ the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial has shown that sorafenib significantly improved overall survival (OS) in patients with advanced HCC, becoming the first agent to demonstrate a survival

benefit in this setting.

Early evidence

Sorafenib is a multikinase inhibitor with activity against Raf kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, FLT3, Ret, and c-Kit. In HCC models, sorafenib exhibited activity that appeared to be related to inhibition of angiogenesis and direct effects on tumor-cell proliferation and survival.² In a phase II study in 137 previously untreated patients with inoperable HCC (72% with Child-Pugh A disease, 28% with Child-Pugh B disease), twice-daily oral administration of 400 mg of sorafenib resulted in partial response in 2.2% of patients, minor response in 5.8%, and stable disease for ≥ 16 weeks in 33.6%.³ Median time to disease progression was 4.2 months, and median OS was 9.2 months. Grade 3/4 drug-related toxicities included fatigue in 9.5%, diarrhea in 8.0%, and hand-foot skin reaction in 5.1%.

Sorafenib vs placebo

In the SHARP trial, 602 patients with advanced measurable HCC, no prior systemic treatment, an ECOG (Eastern Cooperative Oncology Group) performance status of 0–2, and Child-Pugh A status were randomized to receive oral sorafenib, 400 mg twice daily ($n = 299$), or placebo ($n = 303$). The primary study endpoints were OS and time to symptomatic disease progression. The baseline characteristics of the study population are summarized in Table 1.

At an interim analysis performed after 321 deaths (143 in the sorafenib group, 178 in the placebo group), the hazard ratio (HR) for OS in favor of sorafenib was 0.69 ($P = 0.0006$), representing a 44% improvement in OS; this difference met the prespecified criteria for early cessation of the trial. Median OS was 10.7 months in the sorafenib group versus 7.9 months in the placebo group. There was no significant difference between groups with regard to the other primary endpoint of time to symptomatic progression. With regard to secondary endpoints, time to disease progression was significantly improved with sorafenib versus placebo (HR, 0.58; $P = 0.000007$), with median times of 5.5 months versus 2.8 months; rates of disease control (defined as a complete or partial response or stable disease for 2 or more cycles) were 43% for sorafenib versus 32% for placebo.

Sorafenib was well tolerated in the SHARP trial. The frequency of se-

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TABLE 1

Baseline characteristics in SHARP trial

	Sorafenib (n = 299)	Placebo (n = 303)
Median age, years	67	68
Male, %	87	87
ECOG PS = 0, %	54	54
Child-Pugh A status, %	95	98
BCLC stage C, %	82	83

ECOG PS = Eastern Cooperative Oncology Group performance status; BCLC = Barcelona Clinic Liver Cancer

Source: Illovet et al¹

rious adverse events was 52% in the sorafenib group versus 54% in the placebo group; the most frequent grade 3/4 adverse events were diarrhea (11% vs 2%), fatigue (10% vs 15%), hand-foot skin reactions (8% vs 1%), and bleeding (6% vs 9%).

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From the Community Oncologist's Perspective

Sorafenib: new reference standard for systemic treatment of advanced hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the seventh most common cancer in the world. It is estimated that approximately 19,160 new patients will be diagnosed with HCC in the United States this year and that 16,780 people will die from this disease.¹ Moreover, the incidence of HCC is increasing.¹

HCC has been considered relatively refractory to chemotherapy. No definitive treatment has shown a survival benefit in patients with unresectable tumors. Doxorubicin is commonly used for advanced HCC. One controlled study reported a small survival advantage from doxorubicin treatment compared with best supportive care alone (median survival, 10.6 vs 7.5 weeks; $P = 0.036$).² However, there was a 25% rate of fatal complications. In another small trial, combining cisplatin with gemcitabine (Gemzar) yielded an overall 21% response rate, with one complete and nine partial responses.³

SHARP trial

At the 2007 Annual Meeting of

the American Society of Clinical Oncology, a report of a phase III, double-blind, randomized, placebo-controlled trial showed that sorafenib (Nexavar) was an effective systemic treatment for advanced HCC.⁴ In all, 602 patients who had not received prior systemic therapy were enrolled in this multinational study, known as Sorafenib HCC Assessment Randomized Protocol (SHARP). One group of patients was treated with sorafenib, and the other group received placebo. The primary objective was to compare the overall survival of patients in these two groups.

The results showed a median survival of 46.3 weeks in the group treated with sorafenib compared with 34.4 weeks in the control group (hazard ratio, 0.58; $P = 0.000007$). Median time to cancer progression was significantly improved in the group treated with sorafenib (24 weeks) compared with the control group (12.3 weeks). In addition, sorafenib was well tolerated. Diarrhea (11% vs 2%) and hand-foot reactions (8% vs < 1%) were the only grade 3 or 4 adverse events that occurred significantly more frequently

in the treatment arm than in the control arm. The authors concluded that sorafenib improves survival when used as initial therapy among patients with advanced HCC.

These results are groundbreaking because sorafenib is the first agent to demonstrate a survival benefit and manageable side effects in these patients. The National Comprehensive Cancer Network Clinical Practice Guidelines for HCC have recently been updated to include sorafenib as a treatment option for patients (Child-Pugh class A) who have unresectable HCC or decline surgery and are not transplant candidates; have extensive disease, with or without cancer-related symptoms; or have metastatic disease.⁵ Clinicians should take note that the SHARP trial included only patients with a Child-Pugh A status. Therefore, the dosing of sorafenib for patients who have abnormal liver function tests (Child-Pugh class B or C) is unclear. It needs to be determined whether these patients can tolerate the regular dose of sorafenib (400 mg twice a day) or benefit from dose

reduction without compromising its effectiveness.

Conclusion

Sorafenib has become the new standard reference for patients with advanced HCC (Child-Pugh class A), based on the results of the SHARP trial. Another randomized phase II trial comparing sorafenib plus doxorubicin versus doxorubicin alone has been completed. The results are expected to be announced later this year.

We may therefore have more regimens in our armamentarium to fight against HCC in the coming years.

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From the Administrator's Desk

The financial and economic concerns

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The administration and financial cost associated with sorafenib (Nexavar) therapy present issues in regard to patient accessibility. The average monthly co-pay for those patients with commercial insurance who must pay a percentage of the cost of their medications is \$1,100.00. The Nexavar REACH (Resources for Expert Assistance and Care Helpline) Program,¹ a joint provider/patient-assistance program of Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals, Inc., is able to help healthcare providers and patients with both the processing and dispensing of medication.

The average wholesale cost of sorafenib for a 1-month supply (120 tablets) is \$5,416.00. Since sorafenib is not available through retail pharmacies, patients must use a mail-order specialty pharmacy to have their prescriptions filled. A main issue of

concern is the delay in access and initiation of treatment. Patients have to allow at least 24 hours for a benefit investigation to be conducted and then wait for the medication shipment to arrive by mail.

The advantages of enrolling a patient through the REACH Program is that a representative will facilitate the prior authorization (if required), assess for any barriers to treatment, and then link the patient with a mail-order specialty pharmacy for shipment. Uninsured patients are also processed through this program for free drug. The REACH Program offers a financial assistance program for those patients who have co-pays. The level of assistance provided is based upon the patient's total household income. If approved, a 65%–95% deduction is applied toward their co-pay. If a patient is denied assistance through the REACH Program, a list of national

co-pay foundations is provided.

For Medicare patients enrolled in a Medicare Part D plan, a representative from the REACH Program provides verification of benefits. If they have a co-pay or are in their “doughnut hole,” meaning that they are responsible for the entire cost of sorafenib, a representative will provide them with information regarding possible assistance through a co-pay foundation.

Although sorafenib is approved for the treatment of renal cell cancer, some insurance companies have denied coverage due to cost or other extenuating factors. Should this occur, patients may be able to get their medication free through the Nexavar REACH Program.

Reference

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