New Approaches Extend Hepatocellular Ca Survival

BY DOUG BRUNK
San Diego Bureau

LA JOLLA, CALIF. — Improvements in the short- and long-term survival of hepatocellular carcinoma patients are being realized through liver transplantation, surgical resection, and several new therapies, Dr. Donald J. Hillebrand said at a meeting on chronic liver disease sponsored by Scripps Clinic.

Even so, the incidence of hepatocellular carcinoma (HCC) has increased from 1.4 per 100,000 patients in the mid-1970s to 3.3 per 100,000 in 2000-2002. "This disease is on the rise, which is in contrast to most of the abdominal cancers that we deal with on a day-to-day basis," said Dr. Hillebrand, medical director of liver transplantation for the Scripps Center for Organ and Cell Transplantation in La Jolla, Calif.

At the same time, the prognosis for patients with HCC remains dismal. An estimated 90% of all patients with the diagnosis succumb to the disease. "Roughly half of these patients will die of the tumor," he said. "The other half will die from progression of their liver disease. So the more aggressive we are with therapy, the more we push them, but the closer we are to helping them achieve locoregional control."

Dr. Hillebrand emphasized the need for a multidisciplinary approach to HCC. "It can't be just a liver transplant program, because many individuals will benefit from resection," he said. "The hallmark in the middle of all this is the role of the hepatologist. I probably see more HCC than our oncologists, because they come to us in the liver clinic. In general we don't send an individual to an oncologist unless we've exhausted all of the other locoregional treatment options."

The best prognostic group includes patients with a performance status of zero and no constitutional symptoms, Child-Pugh class A cirrhosis, no vascular invasion, and no extrahepatic spread.

Liver transplant "by far achieves the best outcome in patients with decompensated cirrhosis who meet criteria," Dr. Hillebrand said. "Unfortunately, there is a shortage of organ donors available. We can't transplant everybody with HCC."

Surgical resection can be effective in patients without cirrhosis if there is no vascular involvement, because they don't have portal hypertension or hepatic insufficiency. Resection can also be effective in patients with cirrhosis and preserved liver function and relatively early-stage liver cancer. Patients with Child-Pugh class A cirrhosis who have a peripherally located single lesion "can do quite well, with 60% long-term survival," he said.

Dr. Hillebrand noted that candidates for surgical resection should be stratified based on their ability to survive the procedure. "So if the patient has clinically significant portal hypertension or increased serum bilirubin, those are two hallmarks against the ability to tolerate resection," he said.

Indications for surgical resection in patients with no cirrhosis include tumors of any size, as long as there is no microvascular, lymph node, or extrahepatic spread, and resection is technically feasible.

Indications for surgical resection in patients with cirrhosis include having Child-Pugh class A disease, no clinically significant portal hypertension, and a bilirubin level of less than 1 mg/dL. With these criteria, "probably no more than 5% of the HCC that we see in the Western world would be eligible for resection," he said.

Some transplant surgeons are performing portal vein embolization ipsilateral to the tumor to promote hypertrophy of the contralateral lobe. Although this procedure is rare, "there are some data that suggest this may improve the resectability of these tumors," Dr. Hillebrand said. "Usually it's done at major centers that have a tremendous experience with hepatic resection and are more willing to push the envelope."

He pointed out that 50%-75% of patients who undergo surgical resection for HCC will develop a local recurrence or a second primary tumor.

Dr. Hillebrand went on to highlight the following new therapies for HCC:

► **Ablative therapies.** These include chemically mediated forms, such as percutaneous ethanol injection and acetic acid injection, as well as energy-mediated forms, such as cryoablation, microwave ablation, and radiofrequency ablation.

Ablative therapies "can serve as a bridge to transplant," while avoiding upper abdominal scarring. They "provide effective control of the tumor for up to 1-2 years while patients wait for a liver transplant," Dr. Hillebrand said. "For select patients, ablation may offer the same 5-year survival results as surgical resection. The question that hasn't fully been answered yet is, is there initial benefit to tumor reduction, the so-called concept of downstaging?"

► **Locoregional therapies.** These include transarterial chemoembolization, radioactive yttrium-impregnated class microspheres, targeted radiation therapies, laser beam therapies, and cisplatinum gel injection.

One phase II trial of proton beam therapy in 34 patients with HCC and an average tumor size of 5.7 cm demonstrated a 75% local tumor control rate at 2 years (Gastroenterology 2004;127:S189-93).

► **Systemic therapies.** Historically there have been no safe and effective systemic chemotherapy regimens, but two new agents that have been studied are nolatrexed (Thymitaq) and sorafenib (Nexavar).

A recent phase II trial of nolatrexed in 39 patients with advanced HCC showed one partial response for 7 months (Invest. New Drugs 2007;25:85-94). The median overall survival was 32 weeks. "Unfortunately, this was a huge study that turned out to be less than exciting," Dr. Hillebrand said.

A more promising drug is sorafenib, which is approved for renal cell carcinoma. A phase II study of 137 patients showed partial response in 2.2%, minor response in 5.8%, and a delay in time to disease progression of 4.2 months.

Recently, a phase III trial of sorafenib in 602 patients was terminated early because improvements in overall survival were seen. Results of the SHARP trial are expected to be released later this year. ■

Tylenol OD Antidote Has 8-Hour Window

BY BRUCE JANCIN
Denver Bureau

DALLAS — *N*-acetylcysteine for acetaminophen overdose is one of the best antidotes in all of poison control medicine—provided it's given within the right time frame, Dr. Carson R. Harris said at the annual meeting of the Society of Hospital Medicine.

"This is a great antidote. It's virtually 100% effective if given within 8 hours. That's your key, that 8-hour window. A patient can take 3 pounds of acetaminophen—I've had one who tried—and if you start NAC [*N*-acetylcysteine] within 8 hours they'll still probably be okay," said Dr. Harris, director of the toxicology section at Regions Hospital, St. Paul, Minn.

Acetaminophen is one of the most common causes of overdose. That's because acetaminophen is present in more than 200 over-the-counter and prescription drug products, including a plethora of cold and allergy medications.

"We get an acetaminophen level on every altered-mental-status patient who comes in," he said.

Liver damage can occur in adults who take 150 mg/kg of acetaminophen. The hepatotoxicity risk is increased in alcoholics, patients on hepatic enzyme–inducing medications, and in those older than age 45 years.

A serum acetaminophen level of 150 mcg/mL at 4 hours post ingestion warrants NAC therapy. NAC protects the liver and reduces the risk of cerebral edema. It is a free-radical scavenger that binds and neutralizes acetaminophen's toxic metabolite, increases glutathione synthesis, and improves hepatic microcirculation.

'A patient can take 3 pounds of acetaminophen—I've had one who tried—and if you start NAC within 8 hours they'll still probably be okay.'

NAC is approved by the U.S. Food and Drug Administration in both oral (Mucomyst) and intravenous (Acetadote) forms for the treatment of acute overdoses.

The advantages of Acetadote are that it's well tolerated and can be given in a 20- or 48-hour protocol, whereas oral NAC smells like rotten eggs and is approved as a 72-hour treatment regimen.

However, Dr. Harris and other poison control experts use an abbreviated oral NAC schedule that gets most patients out of the hospital in 24 hours. It entails a 140-mg/kg loading dose followed by 70 mg/kg maintenance doses given every 4 hours.

"If the patient is not pregnant and doesn't have any other factors that may cause increased toxicity, you can actually stop treatment after 24 hours if at that point the acetaminophen level is less than 2 mg/L and transaminases are less than two to three times the upper limit of normal. That's what we do. We almost never have patients who take a Tylenol overdose stay in the hospital for 72 hours if they get NAC within 8 hours," Dr. Harris continued.

Oral NAC comes in a 20% solution that should be diluted to 5% in juice or soda. The sulfur odor is a real problem; antiemetic therapy with metoclopramide (Reglan) or ondansetron (Zofran) is often necessary.

Dr. Harris stressed that there's nothing magic about the 20-, 24-, 48-, or 72-hour treatment cutoffs.

"If your patient still feels sick and the liver enzymes are going up, it usually means you got treatment started late. You may have to continue treatment for another 20 hours or so," he explained.

The wholesale cost of enough generic NAC for 24 hours of oral therapy in a 70-kg patient is $18, compared with $430 for Acetadote. ■

Entecavir Not Suited For Patients With Both Hep B and HIV

The antiviral drug entecavir is not recommended for use in patients coinfected with HIV and hepatitis B who are not receiving highly active antiretroviral therapy, because this may promote HIV resistance, according to revised labeling for entecavir.

The black box warning for entecavir now includes the statement that "limited clinical experience suggests there is a potential for the development of resistance" to HIV nucleoside reverse transcriptase inhibitors "if Baraclude is used to treat chronic hepatitis B virus infection in patients with HIV infection that is not being treated."

Baraclude is the trade name for entecavir, marketed by Bristol-Myers Squibb for treating chronic hepatitis B infection in adults.

Other changes in the labeling include the recommendation to offer HIV antibody testing to all patients before starting treatment with entecavir. The changes are summarized in a "Dear Healthcare Professional" letter issued in August by Bristol-Myers Squibb.

—Elizabeth Mechcatie

The letter and MedWatch summary are available at www.fda.gov/medwatch/safety/2007/safety07.htm#Baraclude. Adverse reactions can be reported to the company at 800-321-1335 or to the FDA's MedWatch program.