Liver Cancer Biomarkers Struggling to Succeed

By Steve Benowitz

Liver cancer is an international problem, as the third most common cancer and the fifth leading cause of cancer death worldwide. In the United States, the rising number of cases of the hepatitis C virus (HCV) has helped liver cancer take center stage. It currently is the fastest-growing cancer in incidence in the United States, and it is expected to continue climbing over the next 20 years.

But by the time liver cancer is diagnosed, sometimes after years of chronic hepatitis infection and cirrhosis, treatment options are often limited. Surgical removal is a possibility, if the tumor is small enough, but for some, a liver transplant is the only viable hope. Fewer than 5% of those diagnosed with liver cancer survive for 5 years.

Jorge Marrero, M.D., medical oncologist Paul Brenner, M.D., and their colleagues at the University of Michigan Comprehensive Cancer Center are among doctors across the country looking for biomarkers to detect liver cancer (hepatocellular carcinoma) early, in the hope that screening could lower the rate of death. At first glance, they have an apparent ready-made at-risk population to study: Some 80% of those who develop primary liver cancer are infected with HCV and/or hepatitis B virus, though the cancer can take years, if not decades, to appear.

“Hepatocellular carcinoma is a wonderful model in which to study biomarkers because it is almost unheard of in individuals without hepatitis and cirrhosis,” but most of those infected don’t get liver cancer, said Brenner, who works at the V.A. Medical Center. “We would like to be able to figure out why that is.”

For decades, the most widely used biochemical blood test for liver cancer has been the α-fetoprotein (AFP), a protein normally made by immature fetal liver cells that also shows up in some liver cancer cells. But few researchers have confidence in its abilities as a true biomarker because of its both low sensitivity and specificity.

Most importantly, it has not been shown to decrease the risk of dying from liver cancer. AFP is often elevated for reasons other than cancer, including liver injury, explained Robert Gish, M.D., medical director of the liver transplant program at California Pacific Medical Center in San Francisco, so it doesn’t necessarily indicate the presence or absence of liver cancer.

As in other cancers, the ideal biomarker would be a protein in the blood—and an associated inexpensive blood test—that could predict a range of outcomes at an early stage: who has liver cancer, who is at high risk, whose cancer may recur, and who will respond to treatment.

Efforts to find useful liver cancer biomarkers have been hampered by the same problem that has troubled the general biomarker field for years: poorly designed studies. For example, studies that weren’t large enough, statistically speaking, or didn’t include a diverse enough population have compromised tests’ ability to detect or predict cancer or patient outcome. “As researchers, we tend to fall in love with our own specific, narrow patient population,” said Tim Block, Ph.D., president of the nonprofit, Doylestown, Pa.–based Hepatitis B Foundation, and this can skew findings.

As a result, proposed biomarkers have fallen short of expectations. “There have been no data so far showing that any biomarkers can detect liver cancer earlier,” Marrero said.

Block agreed. “[Liver cancer] biomarker researchers have had a lot of dead ends, a lot of one-paper wonders,” he said.

Biomarkers Abound

Hoping to improve on this track record, a small group of clinicians and scientists from academia, industry, and government gathered recently to discuss more than a dozen potential liver cancer biomarkers at a meeting held by the Hepatitis B Foundation and the National Cancer Institute’s Early Detection Research Network (EDRN).

Several biomarkers are in clinical studies, though only one biomarker is currently U. S. Food and Drug Administration approved: AFP L3, or fucosylated AFP, a slightly different version of AFP. When this marker is elevated, the risk of liver cancer is slightly increased. For those with liver cancer, a high AFP L3 level means a greater chance of recurrence.

Perhaps the two most promising liver cancer biomarkers are DCP and GP73. DCP—des-gamma-carboxyprothrombin—is a precursor of a liver-produced protein that helps the blood clot. In patients with liver cancer, this protein seems to be elevated compared with those without liver cancer. Preliminary studies have suggested that DCP is better than AFP for diagnosing liver cancer and is close to 90% accurate. Marrero is working with a company, Wako Diagnostics in Richmond, Va. (which also makes AFP L3), to develop a panel of biomarkers that includes DCP.

EDRN researchers are organizing large-scale biomarker validation studies for liver cancer that include DCP and, for
comparison, AFP and AFP L3. They are going to test these biomarkers on 450 patients with early-stage liver cancer and 450 control subjects with cirrhosis to see which works best in identifying cancer. They are also collecting enough blood to be able to later test at least 10 new markers.

“We want to encourage researchers to come to us to access these specimens and test their markers,” said Paul Wagner, Ph.D., program director of the NCI’s cancer biomarkers research group, part of EDRN.

“If we find those that work better than AFP, we want to encourage that group to come forward for a prospective screening trial. We want to go to those patients who are coming in for screening and be able to say, ‘Well, this marker is increased, and although we can’t confirm anything by ultrasound, we think it’s very likely that you have cancer.’ We can show that we can detect it early and treat it early. That would be the next step if our markers look good in our validation study.”

Another trial, called HALT-C, is a phase III prospective, multicenter study of patients infected with the hepatitis C virus and advanced fibrosis, some of whom will develop liver cancer. One goal of the study is to evaluate the predictive abilities of DCP and AFP, as well as to identify other biomarkers, Marrero explained.

Block and his colleague Anand Mehta, Ph.D., at Drexel University College of Medicine in Philadelphia, have focused their efforts on GP73, an early-detection biomarker and one of several potential glycoprotein biomarkers for liver disease. In a study of samples from more than 700 individuals at various stages of liver disease, as well as other diseases, GP73 was significantly more sensitive in detecting early- and late-stage liver cancer than was AFP and AFP L3.

**Triaging Biomarkers**

As the researchers know, however, finding biomarkers associated with liver cancer is much simpler than proving that they will actually detect cancer with an acceptable accuracy.

“Appropriate trial design is critical to determine if biomarkers are going to detect cancer earlier or not,” Marrero said, adding that once a marker is found to be useful in early clinical testing, a randomized trial is usually necessary. “It is this level of evidence that will finally determine if biomarkers are helpful or not.”

Marrero and Gish, among others, are skeptical that one biomarker will ever be enough for early detection. They believe that a panel of biomarkers—along with imaging, such as an ultrasound—will ultimately be the solution.

EDRN is hoping to improve the process. While the FDA approval process for biomarkers “isn’t as rigidly defined” as drug approval, Block said, EDRN previously established a five-step validation process that provides a useful roadmap.

“The NCI is helping define and add some structure and predictability to the validation process,” he said. This includes guidelines and tools, along with blinded reference sample sets.

According to Sudhir Srivastava, Ph.D., chief of NCI’s cancer biomarkers research group, researchers can test their potential biomarkers by using reference sets of patient tissue samples from diverse patient populations so that sample bias won’t interfere with findings.

“One way to make rapid progress in triaging biomarkers is to create a reference test,” he said. “We’ve developed a collection of samples that will have cases, controls, and confounders separated and sampled in such a way to provide good statistical power to differentiate between a good, useful biomarker and a bad one. That’s everyone’s goal.”