ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Role of Serum Biomarkers in Hepatocellular Carcinoma Surveillance

Jorge A. Marrero, MD, MS
Keith S. Henley Collegiate Professor of Gastroenterology
Director, Multidisciplinary Liver Tumor Clinic
University of Michigan
Ann Arbor, Michigan

G&H Why would earlier detection of hepatocellular carcinoma be beneficial? What are the consequences if diagnosis is delayed?

JAM First, just to clarify the terminology, screening is a one-time application of a test in a population of individuals who are at risk for a specific disease, while surveillance is a repeated testing performed in order to diagnose a disease earlier. For hepatocellular carcinoma (HCC), the appropriate term is surveillance because repeated testing is necessary to monitor at-risk patients.

Criteria have been proposed to determine if a disease is eligible for a surveillance program. These criteria are: (a) The disease should be an important health problem; (b) There should be a well-defined target population; (c) Treatment of occult disease (ie, disease diagnosed before the appearance of symptoms) should offer advantages compared with the treatment of symptomatic disease; (d) A screening test should be affordable and provide benefits justifying its cost; (e) The test must be acceptable to the target population and to healthcare professionals; (f) There must be standardized diagnostic procedures; (g) Screening tests must achieve an acceptable level of accuracy in the population undergoing screening; and (h) Surveillance should reduce mortality from the disease. For HCC, all of these conditions are met. In terms of the target population for HCC surveillance, we are targeting patients who have compensated liver cirrhosis—especially cirrhosis due to hepatitis C virus (HCV) infection or hepatitis B virus infection.

The goal of a surveillance program is to decrease mortality. In a randomized trial conducted in China, approximately 20,000 people were randomized to HCC surveillance involving α-fetoprotein (AFP) testing and ultrasound or no surveillance. This study showed that patients randomized to surveillance with AFP testing and ultrasound every 6 months had a 37% reduction in mortality compared to patients who did not receive surveillance. This finding is the best evidence that surveillance decreases mortality due to HCC. In contrast, if surveillance is not performed and diagnosis is delayed, patients may be diagnosed at an advanced stage of disease when treatment options are more limited and/or less successful.

G&H How might earlier treatment improve long-term outcomes?

JAM In order for surveillance to be effective, excellent treatment for early-stage HCC is needed. Treatment of small tumors can involve resection, liver transplantation, or radiofrequency ablation. If performed in patients who have small (<3 cm) tumors, these treatments can improve long-term outcomes. Indeed, treatment can often result in

complete response, and these patients have 5-year survival rates above 50%. Thus, the key to successful treatment is to identify patients with early-stage HCC.

G&H What is the current standard of care for HCC surveillance?

JAM The standard of care for HCC surveillance is currently a bit of a controversy. Guidelines from the American Association for the Study of Liver Diseases recommend that ultrasound alone be performed every 6 months. However, randomized trials have shown that the strategy of serum AFP testing combined with ultrasound leads to a reduction in mortality. Also, the combination of AFP testing and ultrasound is the most cost-effective strategy for HCC surveillance. In addition, population-based studies have shown that AFP testing can lead to detection of early HCC, and prospective studies such as the HALT-C study in the United States have shown that ultrasound and AFP testing are complementary. Thus, large amounts of data suggest that the standard of care for the surveillance of HCC should be ultrasound plus AFP testing.

G&H What is the disadvantage of using ultrasonography alone for HCC surveillance?

JAM The problem with ultrasonography is the lack of reproducibility. Ultrasound is operator-dependent, so its reproducibility is poor and has not been studied, which is a major limitation for a surveillance test. In contrast, the major limitation of AFP testing is that this biomarker is not specific to cancer; AFP levels can also be elevated in people who do not have cancer. Given that both tests have different limitations, combining the 2 methodologies may be the best approach, based on cost-effectiveness analyses.

G&H What are the advantages and disadvantages of existing biomarkers for HCC?

JAM In addition to AFP, another biomarker for HCC is AFP-L3. AFP is a glycoprotein that binds to different sugars; in different disease states, the glycoprotein structure of AFP changes and its affinity for various sugars is altered. Studies have shown that the AFP-L3 fraction is more sensitive and specific for HCC than AFP alone. However, the problem with AFP-L3 testing is that the total AFP level must be elevated in order to measure the L3 fraction. Sensitivity is an important feature of any surveillance test, but the sensitivity of the AFP-L3 fraction is always going to be lower than the sensitivity of total AFP testing. Possibly, AFP-L3 testing may have the advantage of being more specific, as this fraction might not be elevated in other disease states. However, ultrasound imaging is also quite specific. Currently, the benefit of AFP-L3 fraction in the surveillance of HCC is unclear.

The other test that is available for HCC is des-gamma carboxyprothrombin (DCP). This test is specific for HCC. DCP testing measures the production of a precursor of prothrombin. In several large prospective studies, DCP has been shown to be similar to AFP in terms of sensitivity, and it may even be complementary to AFP. However, although both AFP-L3 and DCP are approved by the US Food and Drug Administration (FDA), the advantage of using AFP-L3 and/or DCP in combination with ultrasound has not been studied. A study needs to be conducted to determine the complementary nature of the available serum biomarkers—AFP, AFP-L3, and/or DCP—with ultrasound.

G&H You recently published a study in Hepatology on the use of osteopontin for HCC surveillance. Might this biomarker offer an advantage over AFP?

JAM The benefit of osteopontin is that it was identified using a proteomic approach. Plasma was collected from HCV-infected cirrhotic patents with HCC and HCV-infected cirrhotic patients without HCC. Proteomic profiling was performed via a 2-dimensional gel assay. This assay identified several proteins that were different in HCC versus cirrhotic controls. Mass spectrometry led to the identification of osteopontin.

Osteopontin was studied in small cohorts at the University of Michigan and in Taiwan. These cohort studies were case-controlled studies involving patients with cancer and patients without cancer. Most of the patients treated at the University of Michigan were infected with HCV, while the patients in Taiwan were mostly infected with hepatitis B virus. In both groups, osteopontin was better than AFP for identifying patients with HCC.

We then conducted a study in which we collected blood samples from patients and followed these individuals prospectively; 22 patients in this study developed HCC. In analyzing the blood samples from those 22 patients, we found that osteopontin levels were elevated 1 year prior to HCC diagnosis. This is the first paper to identify osteopontin as a novel marker for HCC, but it requires validation. Currently, we are testing the utility of osteopontin in several large cohort studies.

G&H Do you hope to ever perform HCC surveillance using just a biomarker test, or will HCC surveillance always need to include ultrasound?

JAM I doubt we will ever be able to perform HCC surveillance using just biomarker testing. Even if the sen-

sitivity of biomarkers improves, such tests cannot definitively rule out disease. In contrast, if a clinician performs an ultrasound and no tumor or mass is detected, then the patient is very unlikely to have HCC. While we might use different biomarkers in the future, we will likely still combine these biomarkers with ultrasound.

G&H Are any other new biomarkers currently being evaluated?

JAM One approach that looks promising is glycoprotein profiling, which is being studied by several investigators. Glycoproteins are already in use for several tumors, and this is an area that may yield new markers for HCC.

Suggested Reading

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