ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Surveillance for Hepatocellular Carcinoma

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G&H What is the prevalence of hepatocellular carcinoma?

SS Hepatocellular carcinoma (HCC) is becoming increasingly common in clinical practice. As a result, many centers now have dedicated hepatobiliary clinics to manage this epidemic. The increase in HCC is being driven by a large cohort of patients with hepatitis C virus who became infected 20 to 30 years ago and are now presenting to offices with advanced disease. This wave of patients with advanced liver disease from hepatitis C virus will likely be followed by another large cohort of patients with liver damage from fatty liver.

G&H Why is early detection of HCC beneficial? What are the consequences of delayed diagnosis?

SS As with any other serious disease, early detection is critical because it allows for early intervention, which is associated with improved outcomes and quality of life. Patients with HCC detected at an early stage have excellent survival, particularly when they undergo surgical resection or liver transplantation. On the other hand, HCC that is found at an advanced stage is associated with very poor outcomes. Thus, patient outcome depends significantly on the timely diagnosis of HCC, and treatment revolves around the severity of liver disease, tumor burden, and the presence or absence of metastatic disease. Patients who present later in the disease course are more likely to have decreased survival because of the likelihood of vascular invasion and extrahepatic spread of the tumor.

Therefore, early detection is essential to increase survival. Surveillance is important because patients with HCC rarely present with symptoms in the early stages. Patients who do not undergo surveillance for HCC tend to present with more extensive tumor burden and an increased likelihood of metastatic disease. A major issue is that many at-risk patients are not undergoing surveillance for HCC. Studies conducted by my colleagues and I and by Davila and colleagues have shown that this is not only an issue in the community practice but also in other settings.

G&H What are the most common risk factors for HCC?

SS HCC occurs in the setting of "bad soil"—that is, an injured liver. Common causes of chronic liver disease are also common underlying causes of HCC. The most common underlying cause of an injured liver leading to liver cirrhosis and HCC in the United States is hepatitis C virus, and this cause is being trailed, very rapidly, by fatty liver. Hepatitis B virus is also an important risk factor for HCC.

Interestingly, there appears to be a differential risk of HCC depending on the cause of underlying liver disease. For instance, the risk of HCC is much higher in patients who have cirrhosis from hepatitis C virus than, for instance, patients who have cirrhosis from autoimmune hepatitis or primary biliary cirrhosis.

G&H Which patient groups should undergo surveillance for HCC, and how often?

SS Any patient with cirrhosis should undergo surveillance for HCC and should be surveilled twice a year with abdominal imaging. Patients with hepatitis B virus infection should also undergo surveillance depending on their age, gender, hepatitis B viral load, and family history of HCC even if they do not have cirrhosis.

The mode of the abdominal imaging differs among centers. The American Association for the Study of Liver Diseases (AASLD) recommends the use of abdominal ultrasound every 6 months. However, because of the limitations of the operator who performs the study and because of the increasing weight of many patients with fatty liver, many centers fear that ultrasound may not be accurate enough to detect small tumors in obese patients and are alternating an abdominal ultrasound with another image, such as an abdominal magnetic resonance image or an abdominal computed axial tomography scan, every 6 months. In a survey of hepatologists at major liver transplant centers in southern California, my colleagues and I found that most hepatologists were using this strategy. Studies have shown that most hepatologists also supplement abdominal imaging with the measurement of alpha-fetoprotein (AFP) blood values.

G&H Do cirrhotic hepatitis C virus patients who achieve viral suppression still have a high risk of HCC, and should they undergo surveillance for HCC?

SS This is an important issue because viral suppression of hepatitis C virus has become more common with the recent introduction of several new medical therapies. Unfortunately, the answer is yes, these patients still require surveillance for HCC. The major liver societies recommend that even after being cured of hepatitis C, or after having the hepatitis B virus completely suppressed with therapy, patients are still at risk for HCC and should be surveilled appropriately. The risk of HCC may be much smaller in these patients than in patients who have not achieved viral suppression, but nevertheless, the risk is present.

G&H Currently, what is the role of biomarkers for HCC surveillance?

SS The use of biomarkers in this setting is somewhat controversial. Due to concerns about the sensitivity and specificity of AFP, the AASLD decided that the biomarker should not be used routinely for HCC screening and that the most appropriate modality was abdominal ultrasound. However, most hepatologists still use this biomarker because, although the absolute value may not be critical, the trends are. In addition, there are occasional HCCs that do not present as distinct lesions that can be detected by ultrasound; instead, they present as infiltrative tumors, which may not be detectable by abdominal imaging. In these cases, the measurement of AFP may be helpful for detecting HCC.

There is also a good deal of interest in other tumor biomarkers. AFP represents a family of proteins, one of which is AFP-L3. AFP-L3 is a more specific and sensitive HCC tumor marker and is expressed as a percentage of total AFP. Another HCC tumor biomarker is des-gamma-carboxy prothrombin (DCP). DCP is an immature form of prothrombin. The combined use of AFP-L3 and DCP may assist in the diagnosis of HCC. These tumor markers are cleared by the US Food and Drug Administration.

G&H What are the advantages and disadvantages of using biomarkers in this setting?

SS There are many advantages to using biomarkers in clinical practice. Biomarkers are helpful if they are markedly elevated or if there is a trend toward higher values. The diagnosis of HCC is generally made by radiologists. However, tumor markers may help in situations where abdominal imaging is equivocal for cancer; a high absolute AFP value or rising levels of AFP will help support a diagnosis of HCC. As previously mentioned, biomarkers are also helpful when a distinct tumor is not visible, such as with infiltrative tumors, which cannot be seen by ultrasound. These tumor biomarker tests are readily available at most commercial laboratories.

A disadvantage of these biomarkers is that there is not an absolute value that defines the presence of HCC. In addition, many conditions, such as hepatitis B virus and hepatitis C virus, have an inflammatory component to their disease and, thus, may raise AFP levels without being associated with HCC. Another disadvantage is that these biomarkers cannot be used alone for surveillance of HCC; they must be used in combination with ultrasound.

G&H Along with surveillance for HCC, do these biomarkers also have a role in the setting of liver transplant?

SS In addition to allowing for early detection of HCC, these tumor markers are also helpful for surveillance of recurrent HCC in patients waiting for liver transplantation as well as for HCC risk stratification. There is also increasing evidence suggesting that these biomarkers may predict HCC recurrence after liver transplantation.

Very high levels of AFP before liver transplantation may be associated with a poor outcome after the procedure. There are currently a number of ongoing studies looking at these biomarkers and how they may predict outcomes after liver transplantation.

G&H How cost-effective is surveillance for HCC?

SS My colleagues and I performed a cost-effectiveness study and found that surveillance for HCC is cost-effective in a patient with cirrhosis as long as the patient may be considered a candidate for further intervention. Patients can undergo locoregional therapy with radiofrequency ablation and chemoembolization, to name a few treatments, as a bridge to liver transplantation.

G&H What are the next steps in research for HCC surveillance?

SS There are a number of areas that require attention and research. One is spreading the message to providers and their patients that surveillance is necessary for this very serious condition. We also need to develop better models to predict the behavior of HCC. Not all HCCs behave the same; there are some HCCs that are very aggressive and others that are more indolent. Even after liver transplantation, recurrent HCC can directly impact survival. It would be helpful if we could better identify which patients are less likely to benefit from liver transplantation during the evaluation process. We have already identified several factors that are associated with a high likelihood of recurrent HCC, such as vascular invasion seen in the explanted liver.

Dr Saab serves on the speakers bureau for Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals and has spoken on behalf of Wako Diagnostics.

Suggested Reading

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