

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Growing Epidemic of Hepatocellular Carcinoma

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G&H Can the etiology of hepatocellular carcinoma be related directly back to cirrhosis and the underlying diseases that cause cirrhosis? Are there other causes of this cancer?

JM For the most part, hepatocellular carcinoma (HCC) correlates to cirrhosis and its underlying causes. Depending on the geographic area, approximately 80–90% of patients with HCC develop tumors through the development of cirrhosis. The other 10–20% do not have this identifiable risk. Exposure to aflatoxin or polyvinyl chloride can also cause HCC, without any previous history of cirrhosis. However, these cases are very rare. It is possible that genetic mutations may lead to HCC in those without cirrhosis, and ongoing research may answer this question. For the most part, HCC correlates with hepatic cirrhosis.

G&H Could you describe the historic evolution of the viral hepatitis epidemic in the United States and how it relates to escalating levels of HCC?

JM With regard to chronic hepatitis C, the epidemic of infection occurred in the 1960s and 1970s in the United States. That is when the largest percentage of current patients were exposed to the virus, and the majority were, for the most part, in their early 20s at the time. Based on a recent study by Miriam Alter and colleagues at the Centers for Disease Control, the median age of this cohort today is 49 years. In terms of prevalence, approximately 2–4% of the US population is infected, according to the National Health and Nutrition Examination Survey database. Thus, while prevalence has held steady, age and

duration of disease in typical patients have increased, significantly increasing their risk for HCC. As a result, hepatitis C infection is now the main driving force behind the increase in US incidence of HCC. Based on the Surveillance Epidemiology and End Results (SEER) database, the median age of patients with HCC is 63 years. It is therefore expected that as that cohort ages from around 50 years to 60 years and older, the number of cancers will continue to increase.

In the United States, less than 1% of the general population is infected with chronic hepatitis B, another major precursor of cirrhosis and HCC. This level of prevalence is increasing, due to current patterns of immigration, though not necessarily throughout the entire United States. In some metropolitan areas such as the San Francisco Bay and greater Los Angeles, where there are large populations of first-generation Asian immigrants, hepatitis B is an important factor for HCC, as it is endemic in the populations of many Asian countries. However, in areas of the Midwest and other parts of the United States with smaller populations of Asians, HCC related to chronic hepatitis B infection is less of a factor.

G&H Have epidemiologic statistics for viral hepatitis been utilized to predict the course of the current HCC epidemic?

JM Gary Davis at Baylor University has written on hepatitis C epidemiology, predicting a peak in the HCC epidemic occurring 1–2 decades from now, when considering this etiology. Harvey Alter from the National Institutes of Health has a molecular clock study that evaluates the hepatitis C epidemic in the United States. He showed

that the number of hepatitis C–related HCC cases will continue to rise as part of this epidemic.

G&H Do other risk factors need to be factored into models of HCC epidemiology?

JM The SEER database, which provides an excellent snapshot of contributing factors, shows that approximately 30–40% of HCC tumors are found in patients with liver disease of no identifiable cause (ie, no history of viral hepatitis). It has been suggested that these people with HCC but viral-negative markers may have non-alcoholic fatty liver disease. Calle and associates, in their 2003 study of obesity and cancer mortality in the *New England Journal of Medicine*, evaluated the association between obesity and various solid-tumor malignancies. They found that of all the tumors, liver cancer was the tumor most closely related to obesity. This suggests that the current obesity epidemic may continue to raise the prevalence of HCC, even after the epidemic related to viral hepatitis subsides.

G&H How do you predict that the increasing prevalence of HCC will affect the limited pool of donor livers?

JM Donor organs for transplant have remained steady at approximately 6,200 per year for the last 8 years. Attempts have been made to increase the donor pool with living-donor transplant and donation after cardiac death. Despite these efforts, increasing the pool of available, viable organs remains a challenge.

Fortunately, emerging therapies for HCC, such as radiofrequency ablation (RFA), are improving survival, particularly in small tumors and when applied early. The same can be said of partial resection and transarterial chemoembolization (TACE) procedures. In the future, these therapies will be utilized increasingly and transplant will be considered in the event of tumor progression.

For later-stage tumors, we now have a chemotherapeutic option, sorafenib (Nexavar, Bayer/Onyx), which has been shown to improve survival. Sorafenib is also under investigation as an adjuvant therapy or in combination with TACE and RFA or resection. Although these studies are in the beginning stages, they may ultimately

demonstrate additional efficacy for patients, across all tumor stages.

G&H Are more intensive screening and surveillance procedures needed to effectively treat HCC?

JM I do not believe that we need to screen more aggressively, in terms of testing at-risk patients more often. However, there needs to be widespread utilization of surveillance in our patients with cirrhosis, regardless of the cause. Depending on the center, current data show that only 20–40% of cirrhotic patients are actually being screened and are under surveillance. This problem extends to screening for other cancers. Colonoscopy for colon cancer, as an example, is only utilized in about 40% of at-risk patients.

G&H Are there concerns regarding the accuracy of current screening for HCC?

JM The biomarkers that we utilize (alfa-fetoprotein, primarily) are not as sensitive or as specific as we would like for the detection of early-stage HCC. Ultrasound imaging can be very useful but is operator-dependent, leading to potential biases. Well-trained ultrasonographers at high-volume centers have an excellent rate of detection, but at a smaller clinic with lower incidence, the operator may not have enough experience to detect tumors reliably. New biomarkers with greater sensitivity and specificity are needed.

Suggested Reading

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