

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Risk Factors and Treatment for Hepatocellular Carcinoma

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G&H How do the epidemiology and mortality rates of hepatocellular carcinoma compare with those of other major cancers?

RG Currently, the estimated range of new cases of hepatocellular carcinoma (HCC) in the United States is 14,000–18,000 each year. There have been estimates as high as 35,000 yearly cases of HCC in the United States but this number is not as well documented or agreed upon. Regardless, the rate of new HCC development is increasing each year. This is because of the rising demographic of immigrant populations with chronic hepatitis B virus (HBV) infection, as well as the evolving nature of hepatitis C virus (HCV) infection. Rates of HCV infection increased markedly in the 1960s and 1970s and with the natural history of approximately 30 years from infection to the onset of cirrhosis, it is inevitable that HCC will increase as the number of patients with HCV-induced cirrhosis increases. Clearly, HCC is not as widespread as lung cancer but it is among the top 10 causes of cancer death in the United States. Worldwide, prevalence is higher, with approximately 500,000 new cases of HCC per year, making it one of the top three causes of cancer death. The chance of surviving 5 years with untreated HCC is 5%.

G&H How do you determine patients at risk for HCC?

RG Determining at-risk patients can be difficult because the main associated disease states are hepatitis B and hepatitis C and these diseases remain undiagnosed in the majority of infected patients. Of the 1.25–2 million people in the United States infected with HBV, only about 400,000

Table 1. Risk Factors for HCC in HBV-infected Patients

- Male gender
- Coinfection with any other viral liver disease
- Coinfection with HIV
- Alcohol abuse
- Family history of HCC
- Cirrhosis
- Increased liver iron
- Increased alanine aminotransferase levels
- Exposure to aflatoxin B1 food contamination*
- Increased levels of viral replication
- Genotype C HBV infection
- Elevated levels of α -fetoprotein

* Prevalent in improperly stored grains in warm or tropical climates.

HBV = hepatitis B virus; HCC = hepatocellular carcinoma.

are aware of their infection. Approximately 5 million are infected with HCV and only 1 million are aware. It is difficult to screen for cancer in patients who are unaware of the primary associated disease state and awareness and testing for these diseases need to be improved. In patients with cirrhosis unrelated to HBV or HCV, risk factors associated with HCC include increased systemic levels of iron or hemochromatosis, alpha-1 antitrypsin deficiency, and fatty liver disease.

G&H How do you stratify for HCC risk in patients who are known to be HBV- or HCV-infected?

RG HCV patients are at risk for HCC if they have evidence of cirrhosis. For HBV patients, there are a number of factors that can increase the likelihood of developing HCC (Table 1). Patients with any of these risk cofactors should undergo screening.

G&H Could you describe the screening process in at-risk patients?

RG Standard of care in screening for HCC is liver ultrasound at regular 6-month intervals. If no cancer is evident on ultrasound but the patient's level of α -fetoprotein (AFP) is rising, a 4-phase computed tomography (CT) scan is recommended. Testing for elevated AFP has not

proven useful in primary diagnosis in many patients but rising levels are a warning sign for HCC and consistently raised AFP levels indicate a long-term risk of developing HCC. In this regard, AFP testing is also recommended at 6-month intervals, as a gauge of risk rather than a diagnostic tool. Other imaging options to diagnose HCC include magnetic resonance (MR), MR angiogram, and true angiogram.

G&H Are there any potentially curative treatments for HCC?

RG The only high-probability cure for HCC is liver transplantation. There are patients who survive long-term after a surgical resection of HCC but tumors can form elsewhere in the liver. Success rates (cancer-free survival) with resection measure at a maximum of 30–40% at 5 years and at 15–20% at 10 years. Some clinicians consider these rates high enough to serve as an alternative to transplant. I find the opposite to be true. Resection should be considered only when transplantation has been ruled out or in a patient with HCC and no cirrhosis. Patients with drug or alcohol abuse issues are generally refused by the transplant system if they do not go through an abstinence interval with rehabilitation. This can necessitate resection as the only possible option. However, resection in the background of a cirrhotic liver often results in recurrence.

G&H What other therapies are available to prolong life in HCC patients?

RG Ablative methods are the primary form of therapy worldwide due to the complexity of surgery and the shortage of donor organs. These methods include cryosurgically freezing the tumor with liquid nitrogen; administration of intra-arterial chemotherapy, a method of injecting chemotherapeutic agents directly into the tumor via the hepatic artery; radiofrequency ablation, where a probe destroys the tumor by heating it to high levels in a manner similar to microwave but at different wavelengths; and direct injection into the tumor of absolute alcohol that kills tumor cells. Proton beam therapy is also in use but only at one center in Loma Linda, California, to my knowledge.

Systemic chemotherapy with doxorubicin is considered standard-of-care therapy in some oncology practices and is currently under investigation as the control arm in several clinical trials. Other clinicians feel doxorubicin should be dropped from trials, either due to perceived lack of efficacy, lack of data, or a risk of toxicity that outweighs chemotherapeutic benefit. New systemic chemotherapeutic agents that are being tested in humans include sorafenib (Nexavar, Bayer Pharmaceuticals), a RAF-kinase inhibitor, which is being examined in two trials, the first versus treatment with doxorubicin and the

other comparing it to no treatment. Nilotrexed dihydrochloride (Thymitaq) is another systemic therapy that has completed phase III trials but plans for submission to the US Food and Drug Administration were abandoned by the manufacturer when decreased survival was seen in the treatment group compared to doxorubicin as a control. None of these agents are expected, as monotherapy, to provide a cure for HCC. The hope is that some of them may be used in combination and that eventually, along with other agents, they may be able to cure the disease in some cases.

G&H How does diagnosis with HCC affect the model for end-stage liver disease score and patient prioritization for transplant?

RG The model for end-stage liver disease (MELD) score is based on levels of bilirubin, creatinine, and coagulation (INR) that define liver function (creatinine is a surrogate for renal function). Before 2001, one third to one half of liver transplant patients with HCC were removed from the liver transplant list because their tumors grew too large and spread. They were not prioritized unless their physician appealed to the appropriate authorities, which was a complicated and generally unsuccessful task. However, because of the high rate of mortality among HCC patients, the condition was upgraded to between 27 and 29 MELD points. As a result, these patients were prioritized ahead of other patients with progressive liver disease who did not have cancer. Eventually the scoring for HCC was adjusted again, to between 22 and 24 points (with increases every 3 months to ensure that patients receive new organs in a timely manner), where it remains today. In my opinion, this is appropriate because the number of patients currently dying while on the transplant list or disqualified due to the development of an irreversible terminal condition is quite small, and that is great news for HCC patients who fulfill transplant criteria.

Suggested Reading

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