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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Chronic hepatitis B virus infection: Issues in treatment

ABSTRACT

As research continues to define the optimal management of chronic hepatitis B virus (HBV) infection, clinicians must deal with a number of yet unresolved issues: Should we treat all patients with HBV infection to prevent liver cancer, even if they have no evidence of active disease? Which is the best treatment strategy? What do we do with patients who develop resistance to our current drugs? Should we treat patients with HBV infection who have already developed cirrhosis?

A 35-YEAR-OLD ASIAN AMERICAN businessman has been told he has abnormal liver function tests and that he is positive for hepatitis B surface antigen (HBsAg). Ultrasonography has shown his liver to have an irregular surface.

The man is alarmed at these reports. He searches the Internet for answers, and travels to a California medical center to consult with a liver transplant surgeon. The surgeon advises against transplantation because he does not have decompensated disease. Instead, the surgeon starts him on lamivudine (Epivir).

After 4 months of lamivudine treatment, the patient comes to you with several questions:

- Am I likely to develop liver cancer or die from this disease?
- How long will I need treatment?
- I've heard that some people develop resistance to lamivudine. What are my chances of developing resistance?
- Should I continue to take lamivudine or switch to another available option?

These questions point out key issues we currently face when caring for patients with hepatitis.

LIVER CANCER AND HEPATITIS B AND C VIRUSES

Liver cancer is epidemic in the United States and globally. An estimated 400 million people worldwide are chronic carriers of the hepatitis B virus (HBV), which is responsible for the greatest number of cases of liver cancer.[1] Patients with HBV infection may develop liver cancer even without developing cirrhosis.

Some patients with HBV may develop liver cancer even without cirrhosis

According to the Surveillance, Epidemiology, and End Results (SEER) registry, the rate of liver cancer approximately doubled between the late 1970s and 1998.[2] The risk is lowest (but also rising the fastest) in white men. Black men have about double the risk of white men, and men from other racial groups, including Asian immigrants in the United States, have about twice the risk of black men.

Hepatitis C virus is contributing to US cases of liver cancer

In the United States, most of the risk of liver cancer is probably attributable to hepatitis C virus (HCV) infection and its complications: people tend to develop cirrhosis about 20 years after the onset of HCV infection, and liver cancer about 10 years after that.

Molecular modeling studies suggest that HCV came to the United States later than it

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came to Japan. Because the epidemic is ongoing, complications—including cirrhosis, the need for liver transplantation, and liver cancer—are expected to increase in the United States.

Liver cancer risk with chronic hepatitis B virus infection

Beasley et al[3] studied more than 22,000 Taiwanese men with chronic HBV infection for about 10 years during a time when patients were not routinely offered treatment. The lifetime risk of developing cirrhosis or liver cancer was as high as 25% in those who were chronically positive for HBsAg, and the 5-year cumulative incidence of hepatocellular carcinoma was 9%, a rate 100 times greater than in people without the antigen.

Patients who develop cirrhosis from HBV infection have a 5-year survival rate of about 85%. Once decompensated liver disease develops (defined as the onset of ascites, encephalopathy, or variceal bleeding), the death rate increases dramatically, with a 5-year cumulative survival of only about 50%. Many complications and deaths in patients with HBV can be attributed to liver cancer.[3,4]

In HBV with or without cirrhosis, oral agents may slow disease progression

CHRONIC HEPATITIS AND CANCER DEVELOPMENT

Worldwide rates of liver cancer vary widely and probably reflect a range of risk factors that affect the cancer's development.[5] Those at highest risk are those with chronic HBV infection established at an early age.[6] Chronic infection is far more likely to develop if HBV is acquired perinatally rather than later in life (usually acquired sexually). Other risk factors are less well understood, and seven subtypes of HBV are currently recognized, which may affect cancer development, as might naturally occurring toxins such as aflatoxin and others.

Unfortunately, the classic risk factors for hepatocellular carcinoma in patients with chronic HBV infection are outside personal control, ie, male sex, age, and genetic susceptibility. The presence of HBsAg increases the risk nine times. The presence of hepatitis B e antigen (HBeAg) increases the risk 60 times. Other risk factors include exposure to chemical carcinogens, cigarette smoking, and alcohol consumption.

Viral DNA levels. HBV DNA levels may affect the risk of disease complications, progression, and liver cancer. Chen et al[7] followed 3,653 adults who were seropositive for HBsAg with serial ultrasonography and laboratory tests for a mean of 11.4 years during a time when treatment was not routinely offered (1991–2004). During the study, 164 cases of liver cancer were diagnosed and 346 deaths occurred. The risk of developing liver cancer increased with a higher viral DNA level: by the end of the study, patients with the highest levels had a cumulative incidence about 10 times higher than those with the lowest levels. The elevated risk of higher viral DNA level was independent of other risk factors, including sex, age, cigarette smoking, alcohol consumption, and seropositivity for HBeAg.

As a result, reducing HBV DNA levels has been suggested as a target for treatment.

TREATING HBV INFECTION

Newer drugs for treating chronic HBV infection include immune modulators, nucleoside inhibitors, and nucleotide analogue inhibitors.

Immune modulators

Interferons have been used to treat HBV infection since the 1990s. More recently, pegylated interferon alfa-2a (Pegasys), a long-acting form, was approved. These drugs are given intravenously.

Although accompanied by significant side effects, treatment with interferons remains a viable option, as it is one of the few treatments with a clear-cut duration and with the best data about the durability of response to treatment. They are the only drugs that affect the immune system, as well as the virus itself.[8]

Nucleoside inhibitors, nucleotide analogue inhibitors

The development of oral agents to treat HBV infection has been an important innovation. Not only are they more acceptable to patients, but they also have a much lower risk of side effects. Four are approved by the US Food and Drug Administration: lamivudine, adefovir (Hepsera), entecavir (Baraclude), and telbivudine (Tyzeka).

Unfortunately, about 20% of patients who take lamivudine for 1 year develop resistance to it. More specifically, amino acid substitutions occur in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the DNA polymerase of the virus, which renders the drug much less effective. About 70% who take the drug develop the mutation after 5 years. Patients with this mutation may develop hepatitis flares despite treatment.

Studies are under way to test the efficacy of treating HBV infection by combining an immune modulator with a nucleoside or nucleotide analogue inhibitor. Lamivudine with interferon has been studied the most, but studies have not shown lamivudine to provide substantial additional benefit, although sequential or salvage therapy may yet prove helpful.

Defining treatment outcomes

A number of goals could be used for assessing the outcome of treatment of patients with HBV infection:

Biochemical outcomes involve improving liver enzymes, such as bringing the alanine aminotransferase (ALT) level to the normal range.

Virologic end points involve decreasing serum HBV DNA to undetectable levels in unamplified assays (<105 copies/mL) and eliminating HBeAg in patients who initially test positive. The ultimate cure is considered to be the loss of HBeAg and the development of hepatitis B surface antibody, but no drug currently available has proven particularly effective in achieving this.

Histologic improvement, such as the amount of inflammation and fibrosis, may be the best indicator of long-term efficacy. Suggested pathologic scoring systems for determining end points include the Batts and Ludwig scoring system and the Ishak and METAVIR scores. In addition, a reduction in pathology by just two points may be a worthwhile goal.

TREAT EVEN AFTER CIRRHOSIS HAS DEVELOPED?

Our patient has presented with HBV infection, abnormal liver function tests, and, more worrisome, a nodular liver as seen on ultrasonography, which strongly suggests cirrhosis.

Is there any reason to treat someone with HBV infection who has already developed cirrhosis? Some would argue against treatment, since histologic change can no longer be prevented. But a recent study shows that treating patients with cirrhosis is worthwhile.

Liaw et al[9] randomized 651 patients in Asia with chronic HBV infection and advanced fibrosis or cirrhosis without decompensation to receive either treatment with lamivudine 100 mg per day or placebo for a maximum of 5 years. The end points included an increase in the Child-Pugh score (similar to the ABC score used to stratify severity of illness in patients with cirrhosis), the development of decompensation (defined as ascites, encephalopathy, spontaneous bacterial peritonitis, renal insufficiency, or upper gastrointestinal bleeding related to portal hypertension), the development of liver cancer, and death.

The median duration of treatment was nearly 3 years; the study was stopped early due to a significant difference between treatment groups in end points reached. During the study, 34 (7.8%) of 436 patients in the lamivudine group developed end points vs 38 (17.7%) of the 215 patients in the placebo group (P = .001). Patients in the treatment group had almost half the overall disease progression (as assessed by a composite end point score), half the increase in Child-Pugh score, and half the cases of liver cancer compared with those in the placebo group.

Most patients develop resistance to lamivudine within 5 years

Unfortunately, nearly half of the patients in the lamivudine group developed resistance to lamivudine vs only 5% in the placebo group. Perhaps if the emergence of resistance can be prevented with more effective therapy over time, an even bigger impact could be made on reducing the development of liver cancer.

FUTURE INVESTIGATION: MORE QUESTIONS

Recent studies leave us with many unanswered questions about how to manage patients with chronic HBV infection:

- Should all patients with HBV infection be treated to prevent liver cancer, regardless of whether they have evidence of active disease (eg, inflammation on liver biopsy, abnormal liver enzymes)?
- Which is the best treatment strategy?
- Is combining agents justified?
- Could an all-oral regimen be effective?
- If new treatment regimens cause fewer side effects, could we start treating patients at earlier stages of the disease?
- What is the risk of developing mutations that confer resistance to therapy when using drugs other than lamivudine or when using combination therapies?
- What do we do with patients who develop resistance to everything we have available? ■

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