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The Role of Diagnosis and Treatment of Underlying Liver Disease for the Prognosis of Primary Liver Cancer

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Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Underlying chronic liver disease has been associated with an increased risk of developing HCC. This study is a review of the current literature regarding the diagnosis, prognostic significance, and role of treating underlying liver disease in patients who are at risk of primary liver cancer. Relevant peer review of the English literature between 1980 and 2017 within PubMed and the Cochrane library was conducted for scientific content on current advances in managing chronic liver diseases and the development of hepatocellular carcinoma. Hepatitis C virus, hepatitis B virus (HBV), nonalcoholic steatohepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson disease, primary biliary cirrhosis, α 1-antitrypsin deficiency, and certain drugs lead to an increased risk of developing HCC. Patients with underlying liver disease have an increased incidence of HCC. Hepatitis C virus, HBV, and hemochromatosis can directly lead to HCC without the presence of cirrhosis, while HCC related to other underlying liver diseases occurs in patients with cirrhosis. Treating the underlying liver disease and reducing the progression to cirrhosis should lead to a decreased incidence of HCC.

Keywords

liver disease, hepatocellular carcinoma, and cirrhosis

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and develops at a rate of 3% to 4% in patients with liver disease.[1,2] Hepatocellular carcinoma typically occurs in the setting of chronic liver disease and cirrhosis. Hepatitis C virus (HCV), hepatitis B virus (HBV), and hereditary hemochromatosis can directly lead to HCC, while HCC related to other underlying liver diseases is linked to the development of cirrhosis.

These other underlying liver diseases that cause progression to cirrhosis include nonalcoholic steatohepatitis, autoimmune hepatitis (AIH), primary sclerosing cholangitis, Wilson disease, primary biliary cirrhosis (PBC), and α 1-antitrypsin (A1ATD) deficiency. Certain drugs and toxins are also risk factors for the development of HCC. The increased incidence of these underlying liver diseases has contributed to nearly double the age-adjusted incidence rate of HCC in the United States in recent decades.[1]

Several treatment options have emerged for the management of HCC. These include systemic chemotherapy, hormonal

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therapy, targeted therapy, immunotherapy, locoregional therapy, surgical resection, and liver transplant. The focus has shifted toward the treatment of the malignancy without concern of the underlying etiology.[3] The aim of this review is to discuss the underlying liver diseases associated with primary liver cancer and discuss the role of treatment of the primary liver disease as it affects the development of HCC.

Hepatitis C Virus

Chronic HCV is now the most common cause of infection-related death worldwide and approximately 130 to 170 million individuals are currently infected.[4] Untreated, chronic HCV infection can cause deterioration of liver function and leads to hepatic failure. The course of the liver damage is unpredictable and can range from stable liver function to sudden decompensated hepatic failure.[5]

Hepatitis C virus is the dominant cause of HCC in the United States and Europe. As a result, the relationship between HCV infection and the development of HCC has been closely studied.[6,7] It is the persistent inflammation and destruction of hepatocytes that most significantly leads to carcinogenesis. Cell turnover causes poorly differentiated hepatocytes to proliferate and develop into dysplastic nodules and HCC. The degree of inflammation in the liver of patients with HCV also correlates with prognosis once HCC is diagnosed. This makes treatment of underlying HCV critical to outcomes.

There are currently 6 major genotypes (1, 2, 3, 4, 5, and 6) of HCV. Genotype 1, specifically 1a, is the most common in the United States, as it represents 58% of the HCV population. Genotype 1b represents an additional 21%, followed by genotype 2 at 15%, and genotype 3 at 5% of the HCV population. Traditionally, genotypes have played a major role in the selection of treatment options.[8] With the recent surge in newer noninterferon-based therapies, most commonly referred to as direct-acting agents (DAAs), specific medications are chosen based on the genotype, presence or absence of cirrhosis, and presence or absence of NS5A resistance–associated variants. However, there is a now a pan-genotypic DAA, sofosbuvir/velpatasvir, that has been approved for the treatment of genotypes 1 through 6, which can have implications worldwide given the decreased need for expensive laboratory testing and simplicity of treatment.[9] Although current head-to-head studies are ongoing, it appears that achieving sustained virologic response (SVR) is the most important factor for decreased risk of HCC and improvement of outcomes.

A recent meta-analysis of 30 different studies performed by Morgan et al[10] determined that the treatment of HCV strongly reduced the risk of HCC development. Patients who achieve SVR have a lower risk of developing HCC than those who were treated but did not achieve an SVR. Even in the setting of established underlying HCC secondary to HCV, a newly published study found improved overall survival in patients with SVR than those with continued HCV-positive RNA virus loads (15 months vs 9.2 months).[11]

Hepatitis B Virus

An estimated 240 million people worldwide have chronic hepatitis B (CHB), and it is the dominant cause of HCC worldwide.[12] The risk of HCC among patients with HBV is 2% to 5%, and it can develop even in the absence of cirrhosis. However, 70% to 90% of patients with HBV who develop HCC will have cirrhosis. Factors associated with an increased risk of HCC include male sex, increased age, and certain genetic polymorphisms. Because of the association between HBV and HCC, screening for HCC is critical in these patients.

Several studies suggest that the risk of developing HCC is reduced by approximately 50% to 60% following treatment. Lin et al[13] did find a statistically significant risk reduction of HCC with the treatment of underlying CHB (hazard ratio [HR]: 0.31; 95% confidence interval [CI]: 0.15-0.66; $P = .002$). The importance of treating immune-active CHB for overall reduction in HCC is further supported by the completion of a 35-study meta-analysis to include 59 201 participants by Lok et al.[14] Current antiviral therapies aim to suppress HBV replication and reduce viral load, cause the loss of hepatitis B e antigen, and cause the loss of hepatitis B surface antigen. The presence of these antigens has been associated with an increased risk of developing HCC. Practice guidelines set by the American Association for the Study of Liver Diseases (AASLD) recommend the treatment of CHB for patients with immune-active phase disease in an effort to reduce cirrhosis, decompensated liver disease, and HCC. Patients with immune-tolerant CHB are at low risk, and treatment is not recommended per the AASLD guidelines.[15]

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that histologically is indistinguishable from alcoholic steatohepatitis.[16] Incidence of NAFLD is reported to be between 6% and 35% worldwide.[17] The management of NAFLD is based on lifestyle modification, with the goal of reversing factors that can lead to disease progression. Weight loss of 3% to 5% of total body weight has been proven to improve steatosis, and further weight loss of up to 10% has been beneficial in reducing and even reversing inflammation and fibrosis. Medical management of hyperlipidemia, diabetes mellitus, and obesity has also been linked to improved prognosis.[18]

Current research suggests that NAFLD is a preneoplastic condition with overall increased mortality and a high risk of developing cirrhosis with subsequent progression to HCC.[1,19-22] Hepatocellular carcinoma can also develop in the absence of cirrhosis in patients with NAFLD, making it an increasingly difficult disease to manage. The progression of NAFLD to cirrhosis and HCC has been linked to adiposity and insulin dysregulation, suggesting a dynamic process affected by a multitude

of factors.[18,23] It is estimated that 20% of all patients with NAFLD will develop cirrhosis, and 45% of those patients will become decompensated 10 years from the time of cirrhosis diagnosis.

Treatment options for NAFLD are limited. Weight loss of 10% of body weight and exercise can improve steatosis; however, the ideal diet and structured exercise program are not well known. For those who cannot lose weight, bariatric surgery has been suggested as an option, given its ability to improve and even reverse NAFLD.[18] Vitamin E at 800 IU/d should be considered a first-line therapeutic option for nondiabetic patients without cirrhosis, as it has been associated with an improvement in liver histology in this select group. Other therapies such as ursodeoxycholic acid, metformin, and ω-3 fatty acids have not consistently been proven to improve steatosis and are thus not indicated as treatment options of NAFLD.[16] Given its growing incidence and new treatment options for HCV, it is predicted that the most common indication for liver transplantation within the next 30 years will become NAFLD-induced cirrhosis.[23]

Autoimmune Hepatitis

Autoimmune hepatitis is characterized by 4 major factors: chronic liver inflammation, interface hepatitis seen on histology, hypergammaglobulinemia, and the production of autoantibodies-like antinuclear antibodies, anti-smooth muscle antibodies, and liver/kidney microsomal antibodies.[24-26]

Early diagnosis and treatment is critical to avoid progression to cirrhosis and hepatic decompensation. Treatment can be initiated with immunosuppressive medications, with the end points being the normalization of transaminases, reduction in hypergamaglobulinemia, and improvement of histology.

Contradictory to the long-held belief that the risk of malignancy in AIH is negligible, the risk of both hepatic and extrahepatic malignancies still exists. This is particularly true in the setting of cirrhosis.[25,27] The relative rarity of AIH makes it difficult to determine the incidence of HCC, but studies have shown that malignancy can arise as a consequence of both the underlying liver disease and of prolonged immunosuppression for treatment.[25,28] Major risk factors for HCC in AIH include cirrhosis for at least 10 years with decompensation manifested as portal hypertension, immunosuppression for at least 3 years, and male sex. Therapeutic options for HCC in AIH vary according to the size and number of lesions as well as the presence of metastatic disease, but when liver transplantation is an option, it tends to be curative for both AIH and HCC.[29,30]

Other Etiologies

Several other underlying liver diseases can lead to the development of cirrhosis and ultimately HCC. Hereditary hemochromatosis is an autosomal recessive disease in which a progressive accumulation of iron can cause congestive heart failure, diabetes, and cirrhosis.[31] The prevalence of homozygous hereditary hemochromatosis is estimated between 0.26% and 1.89%.[32] Patients with hereditary hemochromatosis with known cirrhosis are at a nearly 20-fold increased risk of developing HCC.[33] Early detection and treatment of hemochromatosis will significantly reduce the morbidity and mortality.

Wilson disease is a rare, autosomal recessive metabolic disorder with an incidence estimated at 1 in 40 000. Although the risk of HCC does not appear to be as great as it is in hereditary hemochromatosis, the risk of liver damage and subsequent progression to HCC have been well-documented. The extent of variability in presentation and pathologic features can be attributed to the heterogeneous nature of genetic variability. Copper overload plays a key role in liver injury and development of cirrhosis, but whether or not there is a direct connection to the oncogenic process is yet to be determined. Prevention of HCC is dependent on early diagnosis and treatment to prevent long-term liver damage.[34]

Primary biliary cirrhosis is an autoimmune progressive cholestatic disease. It initially causes ductal damage by forming granulomas and ultimately leads to the development of cirrhosis. There is conflicting data about the prevalence of HCC in the setting of PBC; however, it has been observed that patients with late stages of PBC (III or VI) had an increased incidence for HCC at 11.1%.[35]

Alpha 1-antitrypsin deficiency causes an abnormal deposition of excessive abnormal α 1-antitrypsin protein in the liver and can ultimately lead to the development of cirrhosis. It is suggested that patients with A1ATD have a higher incidence of HCC and this development can be seen in the absence of cirrhosis.[36-38] Drugs and toxins may also contribute to the pathogenesis of HCC. This progression involves the development of drug-induced liver injury (DILI) that ultimately leads to inflammation, fibrosis, and cirrhosis. The most common classes of medications causing liver injury are antibiotics, antiepileptics nonsteroidal anti-inflammatory agents, immune modulators, and various herbal and dietary supplements. In general, DILI that progresses to liver failure has a very poor prognosis.[39]

Conclusion

The underlying etiology of liver disease plays a significant role in overall prognosis of primary liver cancer. Although it is the rapid progression to cirrhosis that appears to increase the incidence of HCC for patients with underlying liver disease, it is important to understand HCV, HBV, and hereditary hemochromatosis can lead to the development of HCC without progression to cirrhosis. Treatment and management of underlying liver disease should be aggressively pursued in efforts to reduce progression to cirrhosis, which should lead to a reduced incidence of HCC.

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