Review

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Hepatitis B virus-related decompensated liver cirrhosis: Benefits of antiviral therapy

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Summary

Following development of liver cirrhosis in patients with chronic hepatitis B, liver disease may continue to progress and decompensation or hepatocellular carcinoma (HCC) may occur, especially in those with active viral replication. Decompensation may manifest with jaundice, ascites, variceal bleeding or hepatic encephalopathy. Earlier studies have shown that the prognosis of decompensated cirrhosis is usually poor with a 5-year survival rate at 14–35% under conventional standard of care. The approval of oral antiviral agents has greatly improved the prognosis, as demonstrated in several cohort studies and randomized clinical trials involving therapy with lamivudine, adefovir dipivoxil, entecavir, telbivudine, or tenofovir disoproxil fumarate. Oral antiviral agents are effective in restoring liver function and improving survival in patients with decompensated cirrhosis especially if therapy is initiated early enough. These agents are generally well tolerated without significant side effects. However, their preventive effect in HCC development has yet to be convincingly demonstrated. Given their known resistance profiles, entecavir and tenofovir should be considered as the first-line therapy for patients with HBV-related decompensated cirrhosis.

Introduction

Chronic hepatitis B virus (HBV) infection is a serious health problem because of its worldwide distribution and its potential adverse sequelae, including cirrhosis and hepatocellular carcinoma (HCC) [1,2]. It was estimated that more than 200,000 and 300,000 chronic HBV carriers worldwide die of liver cirrhosis and HCC, respectively, each year [3]. Since HBV replication, reflected in the presence of serum hepatitis B e antigen (HBeAg) and/or HBV DNA $\geqslant$2000 IU/ml, may persist after the development of cirrhosis [4], liver disease may continue to progress and hepatic decompensation or HCC may occur. In recent years, remarkable advances have been achieved in the understanding of the natural course after the development of cirrhosis, in the general management of its complications and in the antiviral treatment of this patient population. This review summarizes the advances in general and the benefits of current antiviral therapy in particular.

Natural course after the development of cirrhosis

A substantial proportion of patients with cirrhosis have active HBV replication. A prospective study on cirrhosis detected during long-term follow-up of patients with chronic hepatitis B (CHB) in Taiwan showed that 30% of the 93 patients were seropositive for HBeAg and 73% had a serum HBV DNA level >10,000 copies/ml (2000 IU/ml) at the time of cirrhosis detection with a mean age of 43.6 (24–69) years. During a follow-up period of 12–246 (median 97, mean 102 ± 60) months, hepatitis flare, HBeAg seroconversion, and hepatitis B surface antigen (HBsAg) loss occurred in 32 (34%) of 93, 15 (54%) of 28, and 12 (13%) of 93 patients, respectively; and hepatic decompensation, HCC, and mortality occurred in 12 (13%), 21 (23%), and 11 (12%) patients, respectively [4]. Two earlier studies from Europe showed that 35%-55% of patients with compensated cirrhosis were HBeAg positive [5,6] and 48% of patients in one study were HBV DNA positive (by hybridization) at presentation [6]. HBeAg positivity at presentation was associated with a worse survival and HBeAg or HBV DNA seroclearance during follow-up was associated with a better survival. The cumulative probability of survival at 5 years was 84% for both studies [5,6]. These studies suggest that at least 30–70% of the patients still have active viral replication at presentation of compensated cirrhosis, and that active viral replication is associated with continued liver disease progression and decreased survival over time. By contrast, concurrent hepatitis C virus (HCV) or hepatitis D virus (HDV) infection in HBV-related

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Abbreviations: ADV, adefovir dipivoxil; CHB, chronic hepatitis B; CTP, Child–Turcotte–Pugh; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HRS, hepatorenal syndrome; LAM, lamivudine; LdT, telbivudine; MELD, model for end stage liver disease; Nuc, nucleos(t)ide analogue; SBP, spontaneous bacterial peritonitis; TDF, tenofovir disoproxil fumarate.

cirrhosis may suppress HBV replication despite continuing liver disease progression [7].

Development of HCC

Cirrhosis is the most important risk factor for HCC development. Risk factors for developing HCC in HBV-related cirrhosis include older age, male gender, severity of liver disease, active viral replication during follow-up, viral genotype, viral mutants, concurrent HCV or HDV infection, alcohol intake, and aflatoxin exposure [8]. The risk of HCC in cirrhotic patients is higher in East Asia than in the West, possibly because of earlier acquisition of HBV infection and a longer duration of disease. Combining all data from published studies, the 5-year cumulative incidence of HCC in cirrhotic patients was reported to be 17% in East Asia and 10% in the West [7]. A population-based cohort study in Taiwan showed that baseline HBV DNA level >10^4 copies/ml was the strongest independent predictor of HCC at a dose-dependent manner after adjustment for age, sex, smoking, alcohol, HBeAg status, and serum ALT level. However, the predictive role of baseline HBV DNA level in HCC development in the subgroup of patients with cirrhosis was not reported [9]. Several clinical studies in patients with cirrhosis showed no significant correlation between HBV DNA level or HBeAg status and the development of HCC [4,10,11]. However, two studies from Japan showed a significant correlation between baseline HBV DNA level and the risk of HCC and that persistence of high HBV DNA level (>5000 copies/ml) during follow-up was associated with an increased risk of HCC development [12,13]. The Taiwan study showed that persistent HBeAg seropositivity was related to HCC development with marginal significance ($p = 0.062$) in multivariate analysis [4]. The controversies on the role of baseline viral load and persistence of viral replication in the development of HCC in patients with cirrhosis require further study.

Development of hepatic decompensation

Decompensation usually presents with at least one episode of ascites, jaundice, hepatic encephalopathy (HE) or variceal bleeding [5,10]. Several cohort studies have shown that 2–5% of patients with HBV-related compensated cirrhosis developed decompensation each year [4,10,11]. This can develop insidiously or as a complication of acute hepatitis flare [14,15]. The latter was demonstrated in a study showing that hepatic decompensation developed in 14% of cirrhotic patients who experienced hepatitis flares [14]. These two modes of hepatic decompensation have not been clearly differentiated and compared in terms of prognosis. One study in 161 patients showed that the risk of hepatic decompensation during a median follow-up period of 6.6 years was 4-fold higher in HBV DNA positive patients (13–18%) than in HBeAg negative/HBV DNA negative patients (4%, $p = 0.04$) at entry [11]. Another study of 93 newly developed cirrhotic patients showed that persistent HBeAg seropositivity was significantly ($p = 0.035$) associated with the development of decompensation and the risk of hepatic decompensation during a mean follow-up period of 102 months was 6-fold higher in persistently HBeAg positive patients than in patients who were seronegative for HBeAg at entry [4]. These data suggest that seropositivity for HBeAg or HBV DNA at presentation or HBeAg persistence, reflecting active HBV replication, in compensated cirrhosis is an important factor contributing to further disease progression.

Other than active HBV replication, other hepatitis virus(es) superinfections in HBV-related cirrhotic patients may increase the development of decompensation during the acute phase [16,17] and could be a cause of decompensation during the chronic phase of HCV or HDV superinfection [7,17].

Natural history after the first episode of hepatic decompensation

Earlier European studies showed that the first episode of decompensation most commonly presented with ascites and the prognosis after the development of decompensation was poor, with a 5-year survival rate of 14–35% [5,10,11]. The presenting features of decompensated cirrhosis, its subsequent survival and prognostic indicators were investigated in two Asian studies. A retrospective cohort study involved 96 patients with a median follow-up duration of 3.5 years following the onset of hepatic decompensation. At presentation, the mean age was 54 years and 24% of the patients were HBeAg seropositive. The presenting features were ascites (70%), variceal bleeding (34.3%), jaundice (26%), spontaneous bacterial peritonitis (SBP, 7.3%), and HE (5.2%). Twenty-nine percent of the patients had more than one feature of decompensation. HCC developed in 24 (25%) patients during a median duration of 3 (0.45–7.9) years. The overall 2-year survival rate was 80% after the onset of decompensation. The causes of death were hepatic failure (52.9%), HCC (29.4%), variceal bleeding (5.9%), and SBP (4.4%). HE and hypoalbuminemia ($\leqslant$2.8 g/dl) were significant prognostic factors. HBeAg status was not a significant prognostic factor although serum HBV DNA level was not examined in this study [18]. Another retrospective–prospective cohort study enrolled 102 untreated decompensated cirrhotics with a mean follow-up duration of 46 months. The mean age was 46 years and 28% of the patients were HBeAg seropositive. The presenting features were ascites (63%), variceal bleeding (37%), and HCC (10%). HCC developed in 3% during follow-up. During a median follow-up duration of 13 months, 22 patients died and Kaplan–Meier survival analysis showed a 5-year survival rate of 19%. The causes of death were hepatorenal syndrome (HRS, 32%), variceal bleeding (23%), HCC (28%), liver failure (9%), and HE (9%). Initial decompensation with ascites and development of sepsis with features of systemic inflammatory response were independent predictors of death [19]. Three of the above five studies examined the impact of the HBeAg status on the survival but did not find significant association [5,18,19]. None of the studies assessed the predictive role of baseline HBV DNA level in patient survival. Therefore, the prognostic significance of HBV viremia at the decompensated stage of cirrhosis remains to be studied.

The natural history of HBV-related cirrhosis and decompensated cirrhosis is summarized in Fig. 1 and Table 1.

General management of patients with decompensated cirrhosis

Upon detection or presentation, patients need to be evaluated carefully. The evaluations include liver function status, complete blood cell counts, cause(s) of decompensation (HBV, HCV or HDV), the presence and degree of varices, ascites with or without peritonitis, and HE. The Child–Turcotte–Pugh (CTP) score and