Prevention of Hepatocellular Carcinoma:
antiviral therapy, preneoplastic markers and iron nutrition

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Introduction

Hepatocellular carcinoma (HCC) is perhaps the most prevalent cancer in Asia and West Africa. Globally, 80~85% of HCCs are causally related with HBV, and most of the HBV negative HCCs are attributed to HCV. Approximately 15~40% of the chronically HBV infected individuals die prematurely of cirrhosis and/or HCC.

Fortunately, in most HCCs, 20-40 years will lapse from the time of infection with HBV to the time of developing HCC. As most HCCs are either present with or preceded by chronic hepatitis B (CHB) and/or cirrhosis, effective antiviral therapy, identification of preneoplastic markers and elimination of risk factors in the host, such as high body iron during this period may prevent or delay the development of HCC.

1. Antiviral Therapy

Interferon-alpha (IFN-α) has been available for the past decade for treating CHB. A favorable outcome to IFN-α therapy is associated with factors such as adult-acquired disease, high baseline ALT, low baseline HBV DNA, absence of cirrhosis, and female gender. Most CHB patients, particularly in endemic regions, do not fit this profile and have poor response to IFN-α. It is expensive and often poorly tolerated, and is contraindicated in patients with advanced cirrhosis who are most in need of effective treatment.

Lamivudine (LAM), a nucleoside analog is the (-) enantiomer of 2′, 3′-dideoxy-3′-thiacytidine and has been available for HBV treatment for the past few years. LAM is triphosphorylated within cells and the intracellular half-life of the triphosphate is 17 to 19 hours. Lamivudine triphosphate inhibits reverse transcriptase activity, resulting in chain termination of nascent HBV DNA strands. Thus, lamivudine is a potent inhibitor of HBV replication. LAM eliminates serum HBV DNA, normalizes ALT and improves necroinflammation of the liver. One year of LAM therapy results in HBeAg response rate similar to those obtained with a standard course of IFN-α. Unlike the case with IFN-α, therapeutic responses with LAM are also similar for Asians and Caucasians.

Results of 5 years’ LAM therapy have shown the cumulative HBeAg seroconversion rate of 66-77% among patients
with elevated pre-therapy ALT. Also, the safety and efficacy of LAM has been reported in decompensated cirrhosis resulting from chronic hepatitis B both in Canada and the U.S. In the US multicenter trial, 70 patients with decompensated cirrhosis were treated with LAM 100 mg daily for maximum 142 weeks (median 53 weeks). For patients who received more than 6 months of therapy, there was a gradual increase in serum albumin, and a decrease in serum bilirubin accompanied by improvement in the Child-Pugh score.

The emergence of YMDD HBV variants has been documented. At the end of one-year YMDD variants appear in 14-32% of patients and up to 67% at the end of year 5. Nonetheless, all patients with YMDD variants for more than 2 years had median HBV DNA levels below the pretreatment levels. Histologically, patients with YMDD variants for over 2 years have similar degree of improvement as those without YMDD variants. The long-term clinical effects of the YMDD variants have yet to be determined, but during up to 5 years of follow-up, patients with the YMDD variants tend to maintain partial virologic and clinical response.

Adefovir Dipivoxil (ADV), a nucleotide analog, which has been shown to have potent activity against both the wild type and YMDD variant HBV, is now in phase III clinical trials. ADV was tried alone and in combination with LAM for CHB patients who developed YMDD variant HBV. Interim 16-week analysis has shown suppression of LAM-resistant HBV replication. Fifty-nine patients were randomized to LAM 100 mg qd (n=19), ADV 10mg qd +LAM (n=20), or ADV (n=20). At week 16, the median HBV DNA (log_{10}) change was -0.07 in the LAM arm compared with -2.45 in the LAM+ADV and -2.45 in the ADV. ALT normalized in 42% and 32% in LAM+ADV and ADV recipients respectively, compared with 6% in LAM recipient. Also, addition of ADV to LAM in decompensated CHB with YMDD variant HBV was analyzed at 24 weeks. Median HBV DNA (log_{10}) change was from 8.4 to 4.7 and Child-Pugh score changed from 6 to 5. There was an improvement in serum albumin, bilirubin and ALT. Another placebo-controlled ADV study at 48 weeks demonstrated a significant improvement in histology, HBeAg seroconversion rate, HBV DNA and ALT levels.

Entecavir (ETV) has an inhibitory activity against HBV DNA polymerase. ETV has been tried as double-blind, randomized comparison of 3 doses of 0.01, 0.1 and 0.5 mg once daily vs. LAM 100 mg daily for 24 weeks treatment. The results showed reduction in HBV DNA significantly greater for 0.5 mg than 0.01 mg and 0.1 mg. Superior antiviral activity and ALT normalization of 0.1 mg and 0.5 mg doses of ETV were observed compared to 100 mg LAM. Phase III trial is in progress.

ß-L-2’-Deoxythymidine (LdT) and Emtricitabine (L-FMAU) are also in early stage of clinical trials.

In summary, LAM is a potent, safe and efficacious anti-HBV agent but is associated with development of resistance on long-term use. With other potent nucleoside analogs under investigation and development, the future treatment lies in combination therapies, which may have synergistic or additive antiviral effects and reduce viral resistance.

2. Proneoplastic markers of HCC

HBxAg has long been implicated in hepatocarcinogenesis. During viral replication, the origin of replication for each viral DNA strand consists of an 11-bp direct repeat sequence (DRS). Since the DRS’s are at the end of the growing linear viral DNA strands and overlap the X gene of the virus, the X region is most frequently integrated, and produces mRNA and HBxAg polypeptide. Furthermore, HBxAg is a trans-activating protein that may alter patterns of host gene expression, which is important in tumorigenesis. HBxAg expression correlates with progressive chronic liver disease and with the development of HCC in man and in experimental animals.