Risk Stratification for Patients with Chronic Hepatitis B

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Although the liver diseases that predispose to hepatocellular carcinoma (HCC) and liver failure are well known, not everyone with these diseases will develop these outcomes. Ideally, if it could be predicted accurately who would develop these bad outcomes, treatment strategies to prevent cirrhosis and HCC could be instituted, and screening programmes for HCC could be targeted to the appropriate population.

Among hepatitis B carriers a number of factors have been identified that confer added risk of cirrhosis and HCC. HBV DNA concentration is the best predictor of risk of HCC and cirrhosis. As HBV DNA concentration increases, risk of HCC also increases, with a threshold of risk starting to rise at an HBV DNA concentration somewhere between 104 and 105 copies/ml. This has been shown in several large scale studies. Elevated ALT is also a predictor of increased risk of cirrhosis and HCC, but not as strong a predictor as HBV DNA concentration. Other factors include advancing age, presence of fibrosis on biopsy, hepatitis B genotype C vs genotype B and genotype D vs genotype A. A risk function nomogram providing 5 and 10 year risk for HCC has been developed.

Among cirrhotic patients other factors imply increased risk of HCC or liver failure. These include ongoing viral replication, falling platelet count, and presence on biopsy of several histological markers, such as large cell change, and asymmetric regeneration.

Treatment Goals: Can Chronic Hepatitis B be Cured?

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The ultimate goals for the treatment of chronic hepatitis B is to prevent (or at least delay) the development of cirrhosis complications and hepatocellular carcinoma. It has been shown that prolonged suppression of viral replication with lamivudine can decrease cirrhosis complications and HCC in both patients with cirrhosis and patients without cirrhosis. However, especially in patients who acquire the infection early in life, i.e., most Asian, Mediterranean or African carriers, disease does progress, and complications of cirrhosis and HCC do occur, after HBeAg seroconversion, with HBV DNA levels at relatively low levels (>104 copies/mL or >2000 IU/mL) and ALT levels between 0.5-2 times the upper limit of normal (ULN). Even after clearance of hepatitis B surface antigen (HbsAg), the risk of HCC is not decreased if the patients only lose HbsAg after the age of 50.

The ideal treatment endpoint is HBeAg seroconversion together with permanent suppression of HBV DNA to below PCR detectability and normalisation of ALT levels to <0.5 ULN. As to whether one can consider this as a “cure” for the disease, the fact that patients with HbsAg seroclearance can develop HCC seems to imply a negative answer. However, whether further clearance of covalently closed circular (ccc) HBV DNA in hepatocytes can be considered as a cure has yet to be investigated. That ccc DNA can be lowered with nucleos(t)ide analogue treatment has been documented.

Management of HBV drug resistance

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References


Impact of HBV Genotypes and Mutants in HCC

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420 million people are estimated to be suffering from chronic infection of hepatitis B virus (HBV) and HBV has been a public health problem worldwide, since it was first identified in 1967. Recent studies showed eight genotypes, A–H, of HBV are distinguished by a divergence >8%. Molecular evolutionary analysis in the entire genomic sequence showed association with anthropologic and human migration. One of the most important findings in HBV genotypes is the distinct geographic distributions and their association with different manifestation in hosts. Genotypes A and D are major genotypes in Europe and genotype A has been reported to be associated with chronic liver disease less frequently than genotype D. Nevertheless, subgenotype A1(Aa), mainly in Africa, is suspected to be associated with high prevalence of hepatocellular carcinoma (HCC) with specific mutation in the precore (PC) region which is called Kozack mutation in South Africa. Genotype E is reported to be strongly associated with progression to HBV carrier state during childhood in West Africa and genotype F is localised in the New World. There is still unclear association between HCC specific mutations of genotype E and F. Recently identified genotype G always co-infects with genotype A and is incapable of the processing of HBsAg. The high frequency of the recombination with other genotypes is still unclear in clinical significance. In East Asia, genotype B and C, although the new and genotype C has higher disease-inducing capacity than genotype B with high positivity of HBsAg and mutations in basic core promoter (BCP), CP, and X region. Moreover, genotype B is classified into 2 subgenotypes, B1(Bj) and B2(Ba). Ba is located in Asian countries except Japan and recombined with genotype C in the core and BCP region. Interestingly, determination of cross-resistance profile of each drug has allowed the design of rescue therapy for patients with virologic breakthrough. Early diagnosis and treatment intervention allow the majority of patients to maintain in clinical remission despite the occurrence of drug resistance. Clinical studies are ongoing to determine the best strategy to prevent or delay antiviral drug resistance and its impact on liver disease.

References

Local Ablative Treatment of HCC
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Local ablation treatment is a potentially curative treatment for hepatocellular carcinoma (HCC) not amenable to resection or liver transplantation. Percutaneous ethanol injection (PEI) used to be the main modality of local ablative therapy. In recent years, various thermal ablative therapies such as radiofrequency ablation (RFA), microwave and high intensity focused ultrasound (HIFU) have been developed. RFA is currently the most widely used modality of ablative therapy for HCC. Local ablative therapy can achieve effective local tumour ablation and preservation of normal liver parenchyma. Studies have demonstrated a complete ablation rate of above 90% for liver tumours less than 5 cm in diameter, and a treatment mortality rate of less than 1%. However, the safety of RFA depends on careful case selection and appropriate choice of approaches, which can be percutaneous, laparoscopic, thoracoscopic or open. While RFA is technically simpler compared with surgical resection of liver tumours, there is a learning curve which has to be overcome before RFA can be offered with satisfactory outcome. RFA is currently used mainly for unresectable HCC. It has offered a potentially curative treatment for patients with small HCC but poor liver function due to underlying cirrhosis, who otherwise did not have effective treatment in the past except for liver transplantation. There is some preliminary evidence that RFA may achieve survival results comparable to that of liver resection for small HCCs, although the evidence is not strong enough to recommend RFA as a replacement of resection. A high local recurrence rate is a problem of RFA that requires further research to resolve. Microwave and HIFU are two emerging modalities that may offer some advantages over RFA. It is foreseeable that the role of local ablative treatment of HCC will continue to expand in the near future.