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Direct antiviral agents against HBV and HCV and prevention of liver cancer

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Q. How strong is the evidence that antiviral therapy prevents hepatitis- related hepatocellular carcinoma (HCC)?

The evidence that antiviral therapy prevents hepatitis-related HCC is strong – both for hepatitis B and hepatitis C.

In hepatitis B, treatment with interferon or nucleos(t)ide analogues (NA) has been shown to reduce but not to abolish the relative risk of developing HCC.[1-3] The extent of risk reduction depends among others on the severity of liver damage and ranges from 30% in cirrhosis to up to 80% in non-cirrhotic livers.[3] It is noteworthy that the risk for HCC remains unchanged in patients who develop NA resistance.[1]

In hepatitis C, direct anti-viral agents (DAA) fortunately offer a cure to most affected patients nowadays. The elimination of the virus removes the damaging agent from the liver allowing the organ to regenerate and reducing the risk of hepatitis-related complications. Regarding the treatment-associated prevention of HCC the crucial parameter is cirrhosis. In absence of cirrhosis, patients who achieve a sustained virological response (SVR) may be regarded as cured and have a greatly reduced risk for the development of HCC. In contrast, patients with advanced fibrosis (METAVIR score F3) or cirrhosis are still predisposed to develop HCC, although the risk is significantly reduced in comparison to patients who do not achieve an SVR.[4]

Q. Is chemoprevention influenced by the type of anti-HBV regimen?

The NA entecavir and tenofovir have comparable efficacy and are equally recommended as first-line treatments for patients with chronic hepatitis B.[5] However, a recent Korean cohort study found that tenofovir was associated with a significantly lower risk for HCC compared with entecavir (hazard ratio [HR], 0.61; 95% CI, 0.54-0.70), while all-cause mortality or the need for liver transplantation were also significantly reduced (HR, 0.77; 95% CI, 0.65-0.92).[6] Therefore, these data suggest to prefer tenofovir as first-line hepatitis B treatment in absence of contraindications.

Q. Does treatment of hepatitis improve the management of patients with active cancer?

In hepatitis B, NA treatment suppresses viral replication which stabilises the hepatitis-induced liver disease. This is clinically relevant, since a compensated liver function is essential for the management of HCC regardless of the employed treatment modality.

In hepatitis C, there is not sufficient evidence to recommend antiviral treatment in patients with HCC. However, the positive effect of curing hepatitis C on global liver function provides a rationale to consider antiviral treatment when long-term survival seems feasible. In addition, treatment with DAA appears to be safe and effective in patients with HCC (although SVR rates are lower than in patients without HCC and normal liver function).[7,8]

Q. Does antiviral therapy of HCV favour onset and recurrence of HCC?

The answer is: No. And it would be controversial after our remarks on HCC prevention through hepatitis C therapy if it were otherwise. For HCC prevention and not promoting HCC are two sides of the same coin. So why elaborate on this question explicitly? The reason is that from 2016 onwards several studies were published which reported higher rates of HCC occurrence and/or recurrence following DAA treatment. In addition, the discovered HCCs seemed to display a more aggressive tumour behaviour. In light of these reports, one hypothetical explanation for the increased HCC risk was a distortion of the intrahepatic immune microenvironment caused by the rapid decrease in viral load which would impair immune surveillance and thus favour the growth of pre-existing HCC clones. However, these early studies were limited by retrospective design, rather small patient numbers – particularly considering the heterogeneous patient populations, and fairly short follow-up periods.[9] In the meantime, a meta-analysis has compared the risk of HCC occurrence and recurrence between DAAs and interferon-based therapy and found no difference.[10]

Q. Should patients undergoing anti-viral therapy be kept under HCC surveillance?

The answer to this question depends not only on the type of hepatitis but also on the state of the liver.

For hepatitis B patients, the current EASL guidelines give a two-fold recommendation: Generally, those under NA treatment *should* remain under HCC surveillance (weaker recommendation grade), while surveillance is *mandatory* for those with cirrhosis or with moderate or high HCC risk scores (strong recommendation grade.[5] To assess the HCC risk several scoring systems have been developed (reviewed in[3]), of which REACH-B and PAGE-B are the most prominent scores for Asian and Caucasian patients, respectively. These risk calculators can be used in hepatitis B patients without cirrhosis to tailor the surveillance approach according to patient preferences.

For hepatitis C patients, the current EASL guidelines' recommendation is analogous to the reduction in HCC risk: Patients with advanced fibrosis (METAVIR score F3) and cirrhosis (F4) are strongly recommended to continue surveillance, while those with less affected livers do not require surveillance any longer. [9,11]

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Q. How do co-infections affect antiviral treatment and the risk for HCC in hepatitis B patients?

Chronic co-infections with other hepatitis viruses or human immunodeficiency virus (HIV) increase the risk for HCC in hepatitis B patients. The current EASL guidelines recommend the indicated treatment of co-infections.5 Patients with hepatitis B / HIV co-infection should receive antiretroviral therapy including tenofovir which has antiviral activity against HIV and HBV. In hepatitis B/hepatitis D co-infected patients with ongoing hepatitis B virus DNA replication, NA therapy should be considered. In the case of hepatitis B/hepatitis C co-infection, treatment with DAAs may cause reactivation of hepatitis B. Therefore, in addition to those who fulfil the criteria for hepatitis B treatment HBsAg-positive patients should also be considered for concomitant NA prophylaxis until 12 weeks after DAA intake.

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