Review Article

Concept of HBV and HCV as a Risk Factor and Prevention of Viral Hepatitis-Related Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) represents one of the most common cancers worldwide, and it is a very important reason for cancer-related death. Infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is considered the major leading cause of HCC. The pathophysiology of HB and HC viral-related HCC includes chronic inflammation, deorganization of cell signaling pathways, and oxidative stress. Contrary to HCV, HBV is oncogenic by itself, due to its integration into the DNA of cell. Six months of ultrasound monitoring is recommended for high-risk patients. Using antiviral drugs to manage viral hepatitis decreases the risk of evolution and reoccurrence of HCC. Also, effective preventive measures are very important in decreasing the risk of HCC. The prevention involves primary prevention which is based on HBV vaccination, treatment of acute infection, and eliminating the route of transmission, while secondary prevention is based on using antiviral drugs against HBV and HCV infection to prevent the progress of disease into carcinoma. However, tertiary prevention involves treating the carcinoma to prevent the reoccurrence of the cancer.

Keywords: HBV infection, HCC prevention, HCV infection, hepatocellular carcinoma

Introduction

Carcinoma of the liver is the leading cause of cancer-related deaths worldwide. In 2019 according to the WHO, the universal occurrence of hepatic carcinoma was 4.7% of all cancers.[1]

The most common subtype of carcinoma of the liver histologically is hepatocellular carcinoma (HCC).[2]

According to the age-standardized incidence rate (ASIR) of HCC, the reported cases were higher in East Asia (35.5 cases per 100,000 persons) than in Africa (24.2 cases per 100,000 persons).[3] The most important predisposing factors for developing this type of carcinoma are viral hepatitis (which accounts for 80% of all HCC cases according to the latest epidemiological data), alcohol abuse, non-alcoholic steatohepatitis, and exposure to aflatoxin.[4]

In 2018, there was an increase in the occurrence of hepatocellular carcinoma in persons who were diagnosed as having chronic viral hepatitis. This increase is due to the very small number of people which are undergo screening tests for hepatitis and only a few patients who positive for chronic hepatitis are monitored for carcinoma of the liver, so most patients with carcinoma of the liver (>80%) are usually diagnosed in the middle and advanced stages of the disease.[5]

Hepatitis B Virus (HBV)

This virus belongs to the Hepadnaviridae family. A study conducted in 2015 found that 3.5% of the universal population was diagnosed with hepatitis B infection, making it the most common parentally transmitted infection worldwide.[6] HBV can integrate into the DNA of the liver cells, leading to genomic instability, chromosome reorganization, and mutagenesis in tumor suppressor genes and proto-oncogenes.[7]

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Development of HCC following chronic HBV infection depends on several factors such as viral status (viral load), liver cirrhosis, serostatus, hepatitis B excretory antigen (HBeAg), and others. These parameters are responsible for progression to HCC as well as the response of infection to anti-viral therapies.[8]

The continuous inflammatory process that occurs due to viral infection, results in modulation of the immune response, and premalignant and malignant properties which cause increased proinflammatory cytokines and oxidative stress. These changes instigate necrosis, apoptosis, remodeling of the liver microenvironment, and compensatory regeneration. Fibrosis of the liver which usually occurs by activation of the stellate cells of the liver is an additional factor that contributes to HCC development.[9,10]

Hepatitis C Virus (HCV)

This virus belongs to the Flaviviridae family. In 2017 according to WHO, there were 58 million persons were diagnosed as having chronic HCV infection.[11] In these persons, when there is an increment in the fibrosis of the liver, the risk of HCC development gradually increases.[12] The pathogenesis at which HCC is developed in HCV infection patients includes a disorganized system of immunity, chronic inflammation, and changing job of dendritic cells, macrophage, Langerhans, and B cells.[13]

Accumulation of the lipid within hepatocytes is strongly associated with chronic HCV infection,[14] these changes increase oxidation which is found to be connected to tumorogenesis.[15,16] Unlike HBV infection, no vaccine is available for the prevention of HCV infection. However, in the last decade, a new drug was developed named direct-acting anti-viral agents (DAAs) which can cure more than 90% of HCV patients and so reduces the risk of HCC significantly.[17]

Monitoring Patients at Risk

The patients at risk for HCC development are recommended for doing 6-month abdominal ultrasound and these patients include cirrhotic patients and chronic HBV infection with selected criteria (hepatitis B carriers female more than 50 years, hepatitis B carriers male more than 40 years old, and hepatitis B carriers with a family history of HCC).[2] A 3-months screening strategy has no advantage.[18] A high risk of death from HCC is associated with lengthening the interval from 6 months to 1 year.[19]

Increasing HBV DNA serum levels is connected to the high incidence of HCC.[8] But if the value of HBs antigen is low, the incidence has been decreased.[20]

The declivity of liver function test especially alanine aminotransferase levels were found to be largely associated with HCC (P value <0.005).[21] Other serum markers that are used to anticipate the patient at risk are aspartate aminotransferase, fibrosis 4 index, and platelet index.[22]

Prevention

Vaccination and blocking the way of viral transmission have a role in the prevention of infections. Global vaccination has universally decreased the prevalence of HBsAg and prevented 14.2 million cases of chronic HBV infection in children <5 years of age and also prevented >1.3 million deaths worldwide[23,24] and so decreased the incidence of HCC from 0.92 in unvaccinated to 0.23 in the vaccinated group.[25]

The need for vaccination was ignored by many adults. Hepatitis B vaccine should be received by persons with negative HBs Ag and Ab. Heplisva B vaccine was approved by the United States Food and Drug Administration to prevent HBV infection in adults.[26]

It is important to realize that the infection with HBV and its sequel (HCC) can be prevented by taking the vaccine. Every country should evaluate the dangers of HBV and know the potential high-risk groups.[24]

Hampering the transmission of HBV should have greater attention. Perinatal transmission (from mother to baby) is the main way of transmission of HBV infection.[27,28] Tenofovir (an antiviral drug that is used in various countries) is considered the first option in treating mothers from early to late pregnancy.[29]

Breastfeeding carries a very low risk for transmission of HBV infection which is not so high as that of formula milk, as postulate that baby is taken vaccine at birth, so that HBV infected mothers should not be restricted from breastfeeding. The WHO recommended that the babies who take the vaccine should be breastfed, whatever the status of the mother's hepatitis B virus infection.[30]

Breastfeeding is not encouraged only if the mother is in the period of treatment.[30]

In the case of HCV infection, the main preventative approach is the prevention of the transmission route of disease. The main transmission route includes those who have intravenous drug abuse, multiple sex partners, multiple contacts with an HCV-infected person, those who had surgery within the last six months, needle stick injury, and those who had solid organ transplants without screening measures.

Nowadays most hepatitis C vaccine is under continual study and only used to treat HCV infection.[31]

Antiviral Treatment

A promptness to increase the consciousness and treatment of HBV infection was inception by the WHO in 2016, to eradicate viral hepatitis by 2030.[32] Three types of antiviral

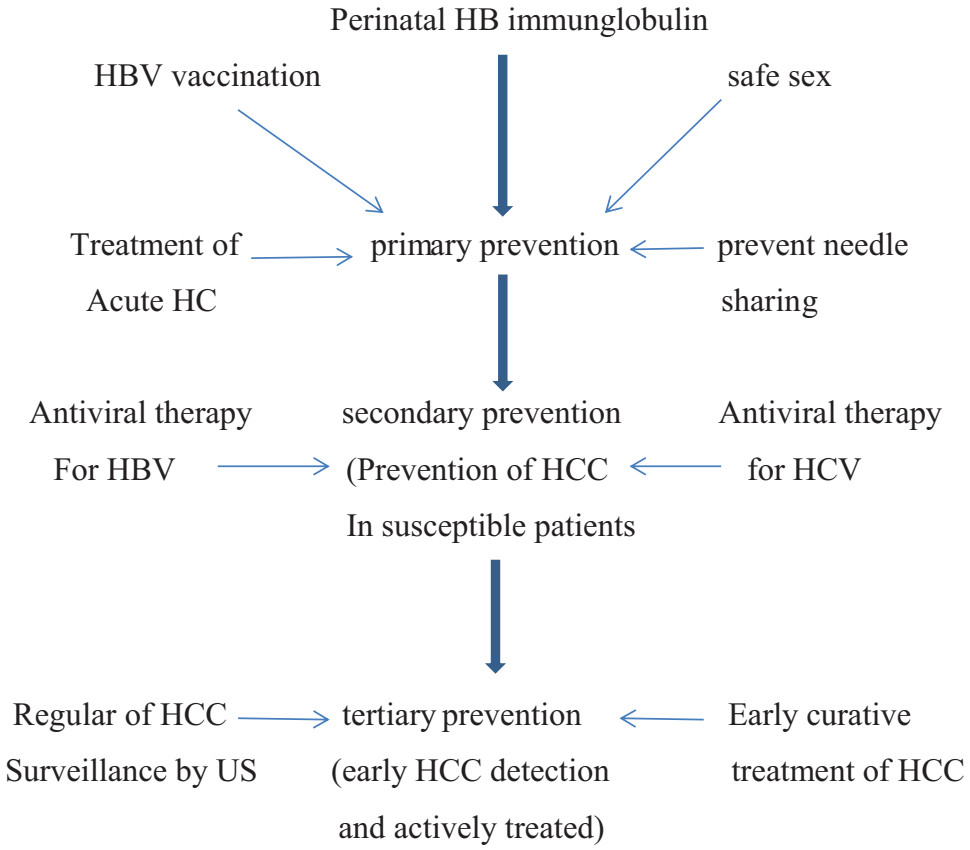

Figure 1: General preventive measures for HCC

drugs (INF and tenofovir (TDF) and entecavir (ETV) are used in the first-line system of treatment of chronic hepatitis B infection.[33] Several previous studies have shown that the use of IFN for a specific period decreases the danger of HCC.[34-37]

Elimination of hepatitis C virus infection is the target for secondary prevention of HCC and there are several studies from the INF region satisfactory shown that the use of SVR (sustained virological response) following IFN decreased the risk of HCC from about 2–8% per year in untreated chronic HCV patients with cirrhosis to 0.5–1% per year.[12,38,39] During the last years, there was a revolution in the HCV treatment landscape by using INF-free DAA drugs because the toxicity of INF encloses the use of it in persons with cirrhosis. SVR is obtained with INF-free DAA drugs in more than 95% of patients and most of them demonstrated improved liver function and fibrosis of the liver.[40] Also, these drugs have minimum side effects and an excellent safety profile.[41]

Conclusion

It is clear from the above review that HBV and HCV infection are considered significant initializing factors for hepatocellular carcinoma's evolution.

The use of HBV vaccination and antiviral drugs against HBV and HCV has resulted in better enhancement of clinical outcomes. These previous procedures in association with preventive measures led to a decrease number of patients who are affected by viral hepatitis in association with cirrhotic complications. HCC monitoring keeps the level of cancer in its early stage and provides effective therapy.

The development of anti-viral therapeutic procedures (against HBV and HCV) that will eradicate the risk of HCC will be under continuing research.

The availability and affordability of preventive measures to people from low- and middle-earning countries will be the goal shortly [Figure 1].

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Conflicts of interest

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