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Current impact of viral hepatitis on liver cancer development: The challenge remains

Viral hepatitis and liver cancer

Abstract

Chronic infections by hepatitis B and hepatitis C viruses are responsible for most cases of hepatocellular carcinoma worldwide, and this association is likely to remain during the next decade. Moreover, viral hepatitis-related hepatocellular carcinoma imposes an important burden on public health in terms of disability-adjusted life years. In order to reduce such a burden, some major challenges must be faced. Universal vaccination against hepatitis B virus, especially at the neonatal period, probably is the most relevant primary preventive measure against the development of hepatocellular carcinoma. Moreover, considering the large adult population already infected with hepatitis B and C viruses, it is also imperative to identify these individuals so to give them access to treatment. Both hepatitis B and C currently have highly effective therapies, which are able to diminish the risk of development of liver cancer. Finally, it is essential for individuals at high-risk for hepatocellular carcinoma to be included in surveillance programs, so that tumors are detected at an early stage. Patients with hepatitis B or C and advanced liver fibrosis or cirrhosis certainly benefit from being followed in a surveillance program. Since hepatitis B virus is oncogenic and capable of leading to liver cancer even in individuals with early stages of liver fibrosis, other high-risk groups of patients with hepatitis B are also candidates for surveillance. An effort must be put into these strategies in order to decrease the incidence and the mortality of viral hepatitis-related hepatocellular carcinoma.

Key Words: Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Epidemiology; Vaccination; Surveillance

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Core Tip: Hepatitis B and C are associated with most cases of hepatocellular carcinoma, and it is estimated that this scenario will remain for the next decade. This review will approach the impact of viral hepatitis on the development of liver cancer, the characteristics of viral hepatitis-related hepatocellular carcinoma, and the challenges that must be faced in order to reduce their burden.

INTRODUCTION

Viral infections are the leading cause of hepatitis, with hepatitis B virus (HBV) and hepatitis C virus (HCV) being the most important causes of chronic viral hepatitis worldwide. There were estimates of near 292 million individuals with chronic HBV infection in 2016 (prevalence of 3.9%) and 71 million people with chronic HCV infection in 2015 (prevalence of 1%)^[1-3]. Hepatitis D virus (HDV) is a defective virus, requiring HBV coexistence in order to replicate. It was estimated that HDV caused chronic infection in approximately 12 million individuals in 2016^[4]. Most of HBV, HCV and HDV infections concentrate in low- and lower middle-income countries^[3].

Liver cancer has the sixth highest incidence among all malignant neoplasms (905,677 new cases in 2020, an incidence of 11.6/100,000 inhabitants). Moreover, it is the second cause of cancer-related death in the world (830,180 deaths in 2020, mortality of 10.7/100,000 inhabitants)^[5]. Hepatocellular carcinoma (HCC) accounts for approximately 75-85% of primary liver cancers^[6, 7]. HCC develops frequently in patients with cirrhosis, in whom it has an annual incidence of 1-4%^[8]. HBV and HCV currently are the two most important risk factors for HCC development worldwide. This is

reflected by the geographical distribution of liver cancer, which coincides with those of HBV and HCV, predominating in transitioning countries, particularly in Asia and Africa^[6,7,9]. In a systematic review of 260 studies with 119,006 patients with HCC, the seroprevalence of HBV and/or HCV was over 60% in most of the 50 countries which contributed with data^[10]. Furthermore, it is noteworthy that, according to the Global Burden of Disease Study, HBV-related liver cancer was associated with 5.80 million disability-adjusted life years, and HCV-related liver cancer, with 2.88 million disability-adjusted life years in 2019^[11]. The impact of HBV may be further increased by the fact that HCC usually develops at earlier ages in patients infected with this virus^[12].

Despite vaccination against HBV and effective treatments for HBV and HCV, it is estimated that their impact on liver health will remain for the next decade at least. Using data from 195 countries or territories between 1990 and 2017, a recent study proposed Bayesian models to project primary liver cancer incidence through 2030. The authors estimated that the age-standardized incidence rate of liver cancer will increase globally from 11.80 in 2017 to 14.08 per 100,000 inhabitants in 2030. According to the etiology of liver disease, HBV was responsible for 46.5% of cases of liver cancer in 1990 and 42.4% in 2017, and it is estimated that it will be associated with 40.7% of cases in 2030. Regarding HCV, it was associated with 25.2% of cases of primary liver cancer in 1990 and 27.0% in 2017, and it is projected that it will be responsible for 26.8% of cases in 2030^[13]. The aim of this article is to review the current impact of viral hepatitis on the development of liver cancer, the characteristics of viral hepatitis-related HCC and the challenges to reduce their burden (Figure 1).

IMMUNE ASPECTS OF VIRAL HEPATITIS IN HEPATOCARCINOGENESIS

In chronic viral hepatitis, the development of fibrosis, cirrhosis and HCC is linked to the activity of the immune response in the infected liver. Both HBV and HCV uniquely infect hepatocytes and replicate in a non-cytopathic manner. The ensuing liver damage that is observed during the acute and the chronic phase of infection is the consequence of virus-specific as well as non-specific immune activity within the

inflamed liver. Histologically, active phases of chronic HBV and HCV infections are characterized by extensive infiltration around the portal tract areas consisting predominantly of CD4+ and CD8+ T cells, but these cells are incapable of clearing these viruses. Multiple mechanisms have been described that explain the weak activity of CD4+ and CD8+ T cells, and that are the main reasons for persistence of HBV and HCV in the liver, and the slowly progressing liver disease^[14-16]. The mechanisms include impairment of dendritic cells and natural killer (NK) cells, increased production of immunosuppressive cytokines and an increase of the numbers of regulatory T cells. In addition, the continuous exposure of immune cells to high levels of viral antigens for many years further contributes and maintains the persistent infection due to exhaustion of HBV and HCV-specific T cells, which renders these cells functionally impaired mediated *via* triggering of exhaustion markers, such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and others^[17].

In the liver, the balance between immune tolerance and immune activation is normally tightly controlled to ensure efficient elimination of pathogen products and transformed cells. Dysregulation of this balance due to viral infection has severe consequences for the process of immune surveillance that is highly efficient in detection and elimination of transformed cells, and contributes to HCC development^[18]. Also, alterations in lipid metabolisms and the release of reactive oxygen species contribute to tumor initiation^[19].

Interestingly, the status of tumor-infiltrating immune cells in HCC has a high degree of resemblance to those observed in an HBV or HCV inflamed liver: an increased T cell infiltrate is observed in HCC, but the CD8+ T cells are dysfunctional with low production of the cytolytic enzymes granzyme and perforin, low overall cytokine production, and relatively high expression of the exhaustion markers PD-1 and CTLA-4^[20, 21]. In addition, also increased numbers of regulatory T cells and reduced numbers and functionality of NK cells have been reported by many groups^[18, 22, 23]. These immune dysfunctions are generally more pronounced in the advanced HCC stages.

The importance of the immune system in controlling the development and progression to advanced stages of HCC is highlighted by observations that increased T cell infiltrates are associated with improved overall survival in HCC and lower tumor recurrence following resection^[24-26]. Furthermore, the enrichment of exhausted T cells in HCC associates with poorer survival, while higher numbers of infiltrating NK cells associate with better survival. Using cytometry by time of flight (CyTOF) and RNA sequencing, a recent study defined different immune subsets and showed that the tumor microenvironment in HBV-related HCC consisted of a more immunosuppressive and exhausted phenotype with an enrichment of regulatory T cells and resident memory T cells that differs from the non-viral-related HCC environment. The study further demonstrated that regulatory T cells associated with poor prognosis, and memory T cells, with good prognosis^[27].

The crucial importance of the patient's immune activity against the tumor has initiated the development of numerous immunotherapeutic approaches in recent years, all aimed at boosting anti-tumor immunity^[28]. The approaches are diverse and include strategies using peptide vaccines and cell-based therapies. Moreover, therapies aimed at neutralizing exhaustion markers using immune checkpoint inhibitors have shown promising results and PD1 blockade has been approved as therapy for HCC. However, many studies are ongoing to improve therapy success by examining the therapeutic outcomes using different combinations of checkpoint inhibitors.

HEPATITIS B AND HEPATOCELLULAR CARCINOMA

-Implications on hepatocellular carcinoma

Advances in next-generation sequencing technology and integrative studies combining multiomic approaches, encompassing genomic and epigenomic characterization and transcriptome, proteomic, and metabolomic analysis of HCCs have shown that HCC is heterogeneous at the histomolecular level, with variable molecular features and clinical outcomes^[29-31]. While ongoing hepatic inflammation, increased cell turnover, repeated cycles of cell death and regeneration, DNA instability leading to an

alteration in DNA and dysregulation of CpG island methylation are common pathways leading to HCC regardless of the underlying etiology of liver disease^[32], there are HBV specific pathogenesis in HCC development. HBV promotes HCC through viral DNA integration into host genes that can provide a growth advantage to the host cell. HBV has been found to be integrated into or near cancer-related genes^[33, 34]. For example, promoter mutation of telomerase reverse transcriptase (TERT), which is often integrated by HBV DNA, is the most frequent genetic event in HBV-associated HCC. The translated protein products of the viral HBV genome have also been implicated in promoting carcinogenesis. For instance, HBx protein, a regulatory protein required for viral replication, has been shown to regulate hepatocytes proliferation, regeneration and apoptosis by modulating PI3K/Akt-mTOR, STAT3/Nanog, and Wnt/ β -catenin signaling pathways to promote the progression of HCC^[35-37].

-Occult hepatitis B virus infection

Occult HBV infection is a condition where HBV DNA replication occurs in the liver in patients with negative serum HBsAg^[38]. While detection of anti-HBc in the blood indicates prior HBV infection, 20% of patients with occult HBV infection are seronegative for anti-HBc. HBV DNA analysis should be further pursued to confirm the diagnosis^[39]. Occult HBV infection increases the risk of HCC development in patients with or without chronic liver disease, which is thought to be mediated by HBV DNA integration into host genome, the production of pro-oncogenic proteins such as HBx protein, and persistent low-grade necroinflammation leading to fibrosis progression^[39]. Currently, HCC surveillance is not routinely recommended in patients with occult HBV infection in the absence of advanced fibrosis/cirrhosis.

-Hepatocellular carcinoma surveillance in hepatitis B

HCC continues to be one of the leading causes of cancer-related deaths throughout the world and it frequently develops within the context of cirrhosis^[40]. This has also led to the development of guidelines among all the major liver societies for HCC surveillance in patients with cirrhosis given its potential for early-stage cancer detection, which likely links to curative treatment^[41, 42]. Given its high oncogenic

potential and its tendency to develop HCC in the absence of cirrhosis, screening for HCC is indicated in a broader population of HBV patients. All HBV patients with HBV cirrhosis (except for patients with severe liver dysfunction and not eligible for liver transplantation) are recommended to undergo HCC surveillance. Surveillance is also recommended in a selected high-risk population of non-cirrhotic HBV patients, as demonstrated in Table 1^[43].

-Eradication of hepatitis B through vaccination

HBV vaccination is an effective primary prevention method for HCC. The effectiveness of HBV vaccination in reducing HCC incidence was reported in a nationwide population-based study from Taiwan. The study used data from 2 Taiwanese HCC registry systems and showed that HCC incidence was four-fold higher in the HBV unvaccinated cohort than in the vaccinated at birth cohorts. Among the 1,509 patients who were 6-26 years old diagnosed with HCC from 1983 through 2011, 1,343 were born before, and 166 were born after the HBV vaccination program began. Moreover, the relative risks for HCC in patients vaccinated at 6-9 years old, 10-14 years old, 15-19 years old, and 20-26 years old in comparison to those who were not vaccinated were 0.26 (95% confidence interval - CI, 0.17-0.40), 0.34 (95%CI, 0.25-0.48), 0.37 (95%CI, 0.25-0.51), and 0.42 (95%CI, 0.32-0.56), respectively^[44]. Although neonatal HBV vaccination is recommended in most countries, vaccine coverage is still less than 70% in most African countries where the incidence rates of HCC remain high^[45], providing a clear window of opportunity for improvement in primary prevention of HCC^[40].

-Major challenges

Aside from identifying infected patients, offering effective treatment against HBV and surveying those at high risk for HCC, the major challenge in order to reduce HBV-related HCC burden is widening the vaccination coverage against the virus. Despite the increase in vaccination coverage between 2010 and 2018 in 97% of the 194 member states of the World Health Organization (WHO), with an increment from 73% to 84% in the completion of the three-dose vaccination schedule and with a raise from

28% to 42% in the neonatal vaccination coverage in the 108 countries in which newborns are vaccinated, improvements are still necessary^[46]. For instance, vaccination coverage has much to improve in countries such as Nigeria, India and Indonesia, which together are responsible for 50% of HBV infections in children under 5 years of age^[3].

HEPATITIS C AND HEPATOCELLULAR CARCINOMA

-Implications on hepatocellular carcinoma

HCV is one of the most important risk factors for HCC. As previously mentioned, HCV is a non-cytopathic virus, which leads to liver damage through immune-mediated mechanisms. However, the virus itself also plays a role in the development of HCC, which becomes clear when considering, for instance, that HCV genotype 3 is associated with a higher risk of HCC than other genotypes^[47]. The mechanism through which HCV genotype 3 is involved in hepatocarcinogenesis is not completely understood yet, but the down-regulation of the phosphatase and tensin homolog (PTEN) gene, which has a tumor suppressor role, might be implicated^[48].

8 Direct-acting antiviral (DAA) therapy in HCV-infected patients has been shown to reduce all-cause mortality (including liver-related and unrelated causes), as well as the incidence of HCC in patients with cirrhosis^[49]. However, in the subgroup of patients with advanced fibrosis or cirrhosis, the risk of developing HCC after achieving sustained virologic response (SVR) remains high, ranging from 0.3 to 1.8% per year^[50]. For this reason, different guidelines recommend lifelong surveillance for patients with advanced fibrosis or cirrhosis even after SVR^[51]. Interestingly, recent studies have attempted to differentiate subgroups of patients with cirrhosis at the highest risk for HCC after SVR. In an Italian study, the combination of clinical predictors (male sex and diabetes), albumin, and genetics identified high-risk patients for HCC^[52]. Furthermore, it is suggested that changes in liver stiffness measured by transient elastography at 1 and 3 years after the end of HCV treatment could identify patients at low risk for HCC^[53].

-Population screening for hepatitis C

In 2017, the WHO Global Hepatitis Report stated that 71 million people worldwide were infected by HCV^[54]. About 3.5 to 5.0 million of these individuals are children and adolescents, and 2.3 million are co-infected with the human immunodeficiency virus (HIV)^[51, 54]. HCV infection causes approximately 400,000 deaths annually, mainly from cirrhosis-related complications and HCC^[54]. Despite the current availability of DAA therapies with high rates of SVR, the prevalence of HCV infection has not changed. One of the reasons that explain this situation is that only 20% of individuals with HCV infection worldwide are aware of their diagnosis. Another reason is that access to DAA treatments continues to be limited mainly by costs in several countries^[54].

The WHO Global Health Sector Strategy on Viral Hepatitis recommended that an effort should be made in order to increase HCV diagnosis rate to 30% by 2020 and to 90% by 2030^[55]. Overall, HCV screening consists in a universal, one-time, and opt-out screening strategy in adults 18 years of age and older with an upper age limit of 79 years. However, periodic screening tests should be offered to individuals with behaviors, conditions or circumstances associated with an increased risk of exposure to HCV^[51].

Vertical transmission could be present in about 5% of deliveries from mothers with HCV and accounts for the majority of HCV infections in the pediatric population^[56]. Universal prenatal screening for HCV facilitates better identification of at-risk infants who require HCV testing^[57]. This evaluation results in better detection of HCV infection in the pediatric population and enables early therapeutic interventions.

-Eradication of hepatitis C

DAA regimens have a high cure rate for HCV infection^[51]. Furthermore, new formulations have simplified the duration and administration of the treatment. However, in 2015, only 7% of people diagnosed with HCV had started antiviral treatment with DAA^[54]. According to the strategy suggested by the WHO, access to DAA should reach 80% of eligible people by 2030^[55]. After this declaration, access to treatment has improved in different countries. An example is the strategy of Australia,

where more than 80% of the HCV-infected population was diagnosed during the last two decades and where there is currently an unrestricted DAA access program that permits prescriptions by any registered medical practitioner. This allowed for the initiation of DAA treatment in Australia for approximately 70% of the total population with HCV-related cirrhosis between 2014 and 2017^[58].

Simultaneously with screening and therapy access, different preventive measures must be carried out in people capable of transmitting HCV (eg, people who inject drugs) in order to avoid new infections or reinfections in those who have been previously treated successfully. Global coverage of harm reduction programs for people who inject drugs, including needle and syringe programs, currently is less than 10%^[54].

-Major challenges

Currently, the major challenge in order to reduce HCV-related HCC burden is identifying infected patients. The silent course of the early stages of this disease makes this challenge even harder to overcome. Therefore, efforts should be made in order to improve awareness of the population and health care workers regarding the underdiagnosis of HCV^[54]. It is also of great importance to shorten the pathway leading from the diagnosis to the extremely effective treatments against HCV, which could even allow for subgroups of patients to be treated in primary care^[59].

Yet another challenge relates to the coronavirus disease 2019 (COVID-19) pandemic. It is estimated that the impact of the pandemic on the global efforts towards HCV eradication could lead to an excess of 44,800 cases of HCC^[60].

CO-INFECTIONS AND HEPATOCELLULAR CARCINOMA

As previously mentioned, HBV and HCV infections are the most common risk factors for HCC worldwide^[61]. ³ Individuals living with HIV are a high-risk population for developing HCC, mostly as a consequence of HCV and HBV co-infection^[62, 63]. Indeed, HCC has become a major clinical problem in HIV. Studies from Europe suggest that the incidence of HCC has risen in HIV-infected patients over the last 20 years, and in Spain alone ³ HCC is the second cause of death in HIV-HCV co-infected patients with

cirrhosis^[64]. Studies from both the United States and Europe suggest that HIV may hasten the evolution of HBV-related HCC, resulting in an earlier age of HCC presentation in HIV co-infected patients^[65, 66].

Although the implementation of new treatments for HCV with DAA agents is expected to decrease HCC incidence, new cases will continue to emerge in the near-medium term^[67, 68]. Moreover, a recent study that reported an HCC risk increase of 1% every year in HIV-HCV co-infected individuals in the HEPAVIR cohort in Europe included in their cohort 61% of individuals with cured HCV, indicating that this population remains at risk for HCC^[63].

In HIV-HBV co-infection, a recent study from the EuroSIDA cohort showed a stable incidence of HCC in non-cirrhotic individuals under HBV therapy (tenofovir specifically), while increasing rates of HCC were seen over time in those not on tenofovir. This suggests a potential threshold to not survey the former group for HCC. However, the same study did show a continued increase in HCC risk among those that had cirrhosis, indicating the importance of surveillance in this population^[69].

Most of the data reported on HIV and HCC originate in resource-rich settings. These dynamics related to poor outcomes are likely to be increased in resource-limited settings, where most of HIV infections occur. A small African study of 60 patients found that those infected with HIV developed HCC at a younger age (32 years) compared to those without HIV (49 years)^[70], and a more recent study from South Africa showed the age of HCC development to be lower in those co-infected with HBV and HIV (mean age of 36 *vs* 46 years in HIV-uninfected). Interestingly, this study showed that females were more impacted by HCC when co-infected with HIV, and the age of HCC presentation was much lower in females with HIV (mean age of 36 years *vs* 50 years in HIV-uninfected)^[71]. In South America and Asia overall, data are scarce on the interrelation between HCC and HIV infection. The specific mechanisms underlying younger HCC occurrence in co-infected individuals with viral hepatitis and HIV is unclear. However, a large Swiss study found a direct association between CD4⁺ T cells and risk of

developing HCC, suggesting that impairment of the immune system could be implicated^[72].

Surveillance for HCC represents a major challenge in co-infected populations not only due to the complex nature of dual disease, but also because most guidelines are tailored towards mono-infected individuals at risk for HCC. In addition, recent studies show that ultrasound surveillance has a low performance for HCC in HBV or HCV individuals co-infected with HIV, with a suboptimal 43% rate of early-stage diagnosis, compared to 63%–71% found in studies on HIV-uninfected cohorts^[73, 74].

Triple co-infection of HIV, HBV and HDV is rather uncommon, ranging from 1% to 20% depending on the geographical area^[75]. However, studies performed in small cohorts have shown that the main impact of HDV to HBV-HIV disease is an accelerated pace to cirrhosis and hepatic decompensation^[76]. In this context, a Swiss HIV cohort reported a 9-fold increase in HCC in those triple co-infected with HIV-HBV-HDV compared to HDV-negative individuals^[77].

CONCLUSION

Despite the advances in prevention and treatment of viral hepatitis, it is clear that many challenges remain in order to reduce the burden of viral hepatitis-related HCC. Universal neonatal vaccination against HBV, as well as vaccination of at-risk adult populations, screening for HBV and HCV, and access to highly-effective treatments against both viruses are instrumental measures that must be pursued with the objective of diminishing their impact on global health and particularly on the development of HCC. Finally, effective surveillance for HCC must be offered to patients who already have advanced fibrosis or cirrhosis and to high-risk HBV-infected individuals, so that HCC is detected at earlier stages, allowing for curative treatments and longer survival.

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