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Commentary

Chronic Hepatitis B and Hepatocellular Carcinoma: Novel Therapeutic Concepts

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Abstract

Hepatitis B virus (HBV) is a partially double-stranded hepatotropic DNA virus that currently infects about 4% of the population worldwide (ca. 296 million people) with the highest prevalence in Asia and Africa and more than half a million deaths annually. Clinically, HBV infection can be asymptomatic with normal or near normal aminotransferase levels or with elevated alanine aminotransferase levels, significant necroinflammation and eventually progression to advanced liver cirrhosis and hepatocellular carcinoma. Indications for treatment of chronic hepatitis B are HBV DNA levels >2000 IU per milliliter and liver cirrhosis. Different from the now available curative oral therapies of chronic hepatitis C by direct-acting antiviral agents (DAAs), to date there exists no curative therapeutic strategy for chronic hepatitis B. Therefore, multiple new investigational therapeutic antiviral concepts are currently explored.

Globally, HCC is the sixth most diagnosed cancer and the third leading cancer-related death in 2020. The management of HCC is complex and depends on the stage of the disease at the time of diagnosis. HCC is largely chemotherapy-resistant and no systemic treatments improved survival until recently. In the early 2000s HCC treatment was revolutionized by sorafenib, a modestly effective orally available tyrosine kinase inhibitor (TKI). In 2018 levantinib was also approved as first-line treatment, followed by several antiangiogenic agents, including among others regorafinib, ramucirumab, and cabozantinib as second-line treatments. Unfortunately, 5-year overall survival of advanced or metastatic disease is still <10%. Therefore, numerous clinical trials are ongoing, assessing immune checkpoint inhibitors (ICIs) in combination with each other or with targeted agents in the treatment of HCCs. Further, ICI incorporation into the treatment of very early-stage HCC by resection or ablation may lower recurrence rate or even cure these patients.

Abbreviations: CHB: Chronic Hepatitis B, HBV: Hepatitis B Virus, HCC: Hepatocellular Carcinoma, ICI: Immune Checkpoint Inhibitors, TKI: Tyrosine Kinase Inhibitor

Introduction

Hepatitis B is a major global public health problem. Hepatitis B virus (HBV) causes acute and chronic infection. The long-term consequences, i.e. liver cirrhosis and hepatocellular carcinoma (HCC) arising from chronic HBV infection carry a risk of premature death in 25% of individuals. The World Health Assembly adopted in 2016 the WHO Global Health Sector Strategy on Viral Hepatitis (WHO-GHSS) aiming at a 30% reduction of new hepatitis B infections and a 10% reduction of HBV-related deaths by 2020 and a 95% reduction of new HBV infections and a 6% reduction of HBV-related deaths by 2030, compared to the baseline year 2015 [1-4]. Vaccines, virus testing and antiviral therapies already exist to prevent HBV infection as well as HBV-related disease progression. While new cases of hepatitis B have been reduced by vaccination [1], HBV-related deaths are expected to rise under the current pace of testing and the available treatment interventions. The same holds true for the early detection of advanced hepatocellular carcinoma and the medical treatment of advanced tumor stages.

In the following novel concepts for the medical treatment of chronic hepatitis B and of advanced HCC will be discussed.

Novel Antiviral Strategies against Chronic HBV Infection

HBV infects and replicates in hepatocytes after it binds to the cell surface via the pre-S glycoprotein and interacts with the hepatic bile acid transporter sodium taurocholate cotransporting polypeptide. The relaxed circular DNA genome is transported to the nucleus and converted to covalently closed circular DNA (cccDNA) that is transcribed into pregenomic RNA which serves as template for reverse transcription into HBV RNA and the translational template for the core protein and polymerase. After the partially double-stranded HBV DNA is enveloped, the virion is secreted or recycles back into the nucleus [2-4].

Therapy of chronic hepatitis B at present rests mostly on pegylated interferons alpha and nucleos(t)ide analogues, such as adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate and tenofovir alafenamide. The nucleos(t)ide analogues result in a sustained viral suppression, improvement of ALT levels and ultimately in a decrease of liver cirrhosis and liver cancer [5,6]. However, even with clearance of serum HBV DNA and hepatitis B e antigen, HBsAg and cccDNA can persist, putting the patient at risk for relapse if therapy is stopped with a potentially severe or even fatal clinical course. To reduce the need for lifelong treatment, novel strategies are

aimed at a functional or complete cure (Table 1). Numerous new anti-HBV compounds that are expected to fulfill these requirements have been or are presently evaluated in clinical studies [2-4].

While none of the antivirals evaluated to date in clinical trials result in a functional or complete cure (Table 2), one can hope that innovative curative therapeutic concepts will be developed in the future. For the time being the major focus will be the worldwide implementation of HBV vaccination, the consequent clinical testing of individuals at risk and the antiviral treatment of those already infected. Given the seminal development of effective drugs against chronic hepatitis C [7], it is hoped that a similar success will eventually eradicate HBV infections and its associated morbidity and mortality.

Table 1: Therapeutic Antiviral Response.

Liver cccDNA	Serum ALT	Serum HBV DNA	Serum HBsAg	Anti-HBs
Virologic +	Variable	-	+	-
Biochemical +	Normal	Variable	+	-
Functional + *	Normal	-/+	-/+	-/+
Cure - **	Normal	-	-	+

* Time-limited therapy, e.g. 1 yr
** Long-term therapy, yrs.

Table 2: HBV antivirals in clinical studies.

Drug	Mode of Action
Myrcludex B	Entry inhibitor
Nitazoanide	HBx target
CRV-431	"
GSK 3228836	RNA degradation
JNJ-3989	"
AB-729	RNAi
ALN-HBV (VIR-2218)	RNA degradation
Vebicorvir	Capsid Assembly Modulator
ABI-H3733	"
ABI-4334	"
Morphodiadin	"
JNJ-6379	"
EDP-514	"
RG7907	"
QL-007	"
ALGH-000184	"
AB-836	"
VNRX-9945	"
O7049839	"
RG7336	iRNA agent
JNJ-3989	" [15]
AB7-29-001	"
VIR-22198	"
ALG-125755	"
Bepirovirsen	Antisense oligo [16,17,18]
ALG-020572-401	"
Nivolumab	Anti-PD-1
Cemiplimab	

Novel Therapeutic Strategies for Advanced Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, the sixth most frequent cancer and the third leading cause of cancer-related death worldwide [8]. HCC is an aggressive tumor that usually occurs in the setting of chronic liver diseases and cirrhosis [9]. A widely accepted treatment algorithm has been proposed by the Barcelona Clinic [10]. Depending on the stage of the HCC, treatment options are divided into surgical (resection, cryoablation, liver transplantation) and liver-directed non-surgical procedures (percutaneous ethanol or acetic acid injection, radiofrequency/microwave ablation, transarterial embolization, external beam radiation) and systemic treatment modalities (chemotherapy, molecularly targeted therapy and immunotherapy with immune checkpoint inhibitors (ICIs) [10].

Systemic treatment approaches for patients with advanced, unresectable HCCs in most cases are inappropriate for surgical or liver-directed non-surgical interventions, due the patient's limited hepatic reserve. Unfortunately, in clinical practice >20% of HCCs are detected late, at already advanced stages. Further, HCCs are relatively chemotherapy-refractory tumors.

With a better understanding of the pathophysiology of HCCs, its hypervascularity and vascular abnormalities, the role of proangiogenic factors such as VEGF was identified in the early 2000s. With the development of the small molecule sorafenib, blocking the VEGFR, PDGFR, cRAF1, B-Raf, as orally available tyrosine kinase inhibitors (TKIs) or humanized monoclonal antibodies bevacizumab, cetuximab, e.g., VEGF, EGF, into clinical practice [11,12] this strategy gained momentum]. While the single-agent anti-programmed cell death (anti-PD-1) ICIs resulted in a modest response, the combination of atezolizumab (an anti-PFD-L1 ICI) with bevacizumab (an anti-VEGF antibody) was approved as first-line therapy in 2020. It showed a significant improvement in response rate, progression free survival and overall survival compared to sorafenib, the previous standard of care. This study established the combination of the antibody anti-PD-L1 atezolizumab with the VEGF-Inhibitor bevacizumab as first-line therapy for the advanced HCC. While pembrolizumab and nivolumab were conditionally approved, a decision whether to keep or withdraw the approval is still pending [13,14].

Despite these promising results of the combination of atezolizumab and bevacizumab for advanced HCC, several issues need to be carefully considered, especially the hepatic reserve and possibly the cause of liver disease. Further, a word of caution is in order, regarding the efficacy of multiple combination therapies. A recent study evaluating the combination of siRNA (JNJ-3989) with or without a CpAM (JNJ-6379) had the lowest rate of response compared with the 2 siRNA plus NA for comparison. This raises the possibility of an interaction between CpAM and siRNA and suggests that not all combinations will result in synergy.

Discussion and Conclusion

Chronic HBV infection results in chronic hepatitis with a life-time risk for progression to cirrhosis and HCC. Consequently, life-long

monitoring is required to detect disease progression and surveillance is recommended to identify individuals at increased risk for HCC development. Current therapeutic options against chronic hepatitis B improve clinical outcome, but are not curative because they have no effect on cccDNA and integrated HBV DNA. While to date, none of the numerous therapeutic options (Table 2) have resulted in a functional or curative response. Given the global burden of disease there is an urgent need for more effective therapies, increased efforts to identify the patients already infected and to expand the vaccination programs with the aim to eliminate HBV infection worldwide.

With respect to the dismal prognosis of patients with advanced HCC at the time of diagnosis numerous clinical trials are assessing ICIs in combination with each other and with targeted agents. At the same time, major efforts are directed at the earlier detection of HCCs that are amenable to surgical and non-surgical liver-directed therapeutic strategies.

Conflict of Interest

No financial interest or conflict of interest exists.

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