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Carcinoma Pathogenesis and Current Treatment Strategies

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Introduction

Hepatocellular carcinoma is the most common type of liver cancer, with a high mortality rate and a low five-year survival rate, resulting in a significant global burden on healthcare systems. HCC initiation and progression are aided by various etiological risk factors such as hepatitis B and C virus (HCV) infection, non-alcoholic fatty liver disease, and tobacco smoking. Endogenous genetic changes, epigenetics (DNA-methylation, miRNA, lncRNA, etc.), and dysregulation of key signalling pathways all play a role in the development of HCC. The variety and complexity of different pathomechanisms reflect the difficulties in tailoring HCC medical therapy. Treatment options for HCC are determined solely by tumour staging and liver function, as defined by the updated Barcelona Clinic Liver Cancer classification system [1].

Description

For early tumour stages, surgical resection, local ablative techniques, and liver transplantation are all viable and curative therapeutic options. Systemic therapy is advised for multifocal and metastatic diseases. While Sorafenib had been the sole HCC first-line therapy for decades, recent developments have resulted in the approval of new first-line and second-line treatment options. Anti-PD-L1 directed combination therapies, either with anti-VEGF directed agents or with anti-CTLA-4 active substances, have been adopted as the new first-line treatment standard. However, clinical trial data show that different therapeutic regimens have different responses depending on the underlying pathogenesis of hepatocellular cancer. As a result, current international clinical guidelines have re-emphasized histopathological examinations in addition to standardised radiological diagnosis using contrast-enhanced cross-sectional imaging.

On this occasion, the treatment sequences for early and advanced tumour stages are summarised using the recently updated Barcelona Clinic Liver Cancer classification system and the current systemic therapy algorithm (first-, second-, and third-line treatment). Furthermore, as promising treatment options, we discuss novel precautionary and pre-therapeutic approaches such as therapeutic vaccination, adoptive cell transfer, locoregional therapy enhancement, and non-coding RNA-based therapy. As the mainstay of HCC therapy, these novel treatments may extend overall survival rates in terms of quality of life and liver function [2,3].

Liver cancer is one of the world's major health issues, and high diagnostic and medical care standards are recommended. With 905,677 new cases per year in 2020, liver cancer was the sixth most common cancer. Despite advances in diagnosis and treatment, liver cancer mortality remains high. With 830,180 deaths per year, liver cancer is the second most lethal tumour after pancreatic cancer. Only 18% of patients survive five years. Hepatocellular carcinoma is the most serious tumour entity among primary liver tumours. It accounts for between 75% and 90% of all cases. Following HCC, intrahepatic cholangiocarcinoma is the second most common entity, accounting for 10%-15% of all cases. There are also uncommon types of primary liver cancer, such as fibrolamellar carcinoma, angiosarcoma, and hepatoblastoma.

Regardless of the aetiology (hepatitis C virus (HCV) infection, hepatitis B virus infection, metabolic syndrome, chronic alcohol abuse, hemochromatosis, or 1-antitrypsin deficiency), liver cirrhosis is the most common cause of HCC. HCC will develop in approximately one-third of all patients with liver cirrhosis over their lifetime. HCC develops in approximately 2% of patients with HBV-associated liver cirrhosis each year, and in 3-8% of patients with HCV-associated liver cirrhosis. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), in addition to viral hepatitis, have emerged as significant risk factors for HCC in recent years, but with a high heterogeneity of newly diagnosed HCC each year.

Hepatitis C virus (HCV) infection, hepatitis B virus infection, metabolic syndrome, chronic alcohol abuse, hemochromatosis, or 1-antitrypsin deficiency are the most common causes of HCC. Over the course of their lives, approximately one-third of all patients with liver cirrhosis will develop HCC. Each year, approximately 2% of patients with HBV-associated liver cirrhosis develop HCC, and 3-8% of patients with HCV-associated liver cirrhosis develop HCC. In recent years, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), in addition to viral hepatitis, have emerged as significant risk factors for HCC, but with a high heterogeneity of newly diagnosed HCC each year.

Systemic therapy is recommended in cases of multifocal tumour manifestation, macrovascular portal vein invasion, extrahepatic tumour spread (BCLC stage C), or slightly reduced performance status (ECOG 1-2). In the first line setting of systemic therapy, physicians select either tyrosine kinase inhibitor (TKI) therapies such as sorafenib and lenvatinib, or immune-oncological (IO) approaches such as atezolizumab and bevacizumab or durvalumab/tremelimumab. Subgroup analysis in the pivotal trials revealed that patients with HCC secondary to viral hepatitis were the primary beneficiaries of the start of IO-based therapies. Patients with HCC caused by NAFLD or NASH, on the other hand, appeared to benefit more from TKI therapy, such as lenvatinib or sorafenib.

With regular alcohol consumption, inflammatory processes, hepatocyte necrosis, and regenerative processes associated with oxidative stress condition the development of hepatic cirrhosis. Alcohol consumption is commonly associated with HCCs in viral hematogenesis. This also emphasises the additive effect of alcohol abuse and HBV or HCV disease. A prospective study in patients with chronic HCV infection and liver cirrhosis found a significantly increased HCC risk, even with concurrent mild to moderate alcohol consumption, with a cumulative 5-year HCC incidence of 23.8%. In contrast, the incidence of HCC in patients who did not consume any alcohol was only 10.6%. Even in the absence of infection, alcohol is a major risk factor for HCC pathogenesis [4,5].

Conclusion

For many years, the BCLC classification has been the gold standard

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for classification and stage-based therapeutic algorithms in the clinical management of HCC. For intermediate stages, therapeutic options include surgical resection, local ablative therapies, transarterial chemoembolization, and radioembolization. For tumour nodules that meet the extended MILAN criteria in their early stages, liver transplantation is considered. Clinical decisions should be based on a multidisciplinary board discussion that includes all disciplines as well as local expertise. Systemic therapy with expanding therapeutic options and targets is recommended for BCLC stage C patients. Unfortunately, no predictive biomarker (except for elevated serum AFP for ramucirumab) has been linked to the therapeutic response to any therapeutic agent.These circumstances highlight the need for more translational research and highlight the unmet need for additional molecular driver-targeted therapies. We summarised the molecular pathogenesis of HCC in relation to current "druggable" systemic HCC treatment options.In the future, more efforts will be required based on human histopathological tumour specimens, which must be obtained not only for diagnosis but also to tailor personalised medicine in HCC.

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