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Current Perspectives on Hepatocellular Carcinoma: Summary and Evidence-Based Recommendations

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Abstract: When cancerous cells grow inside the liver's tissues, this is called primary liver cancer. Primary liver cancer is different from metastatic cancer, which starts in another part of the body and spreads to the liver. The liver is one of the body's largest organs. Hepatocellular carcinoma (HCC) can be caused by liver cirrhosis, infections with hepatitis B and C viruses, excessive alcohol consumption, exposure to aflatoxin B1, and non-alcoholic steatohepatitis. Hepatocellular carcinoma is the fifth most common cancer worldwide and the second leading cause of cancer-related deaths. Chronic infections with hepatitis B and C viruses are the primary causes of hepatocellular cancer. About 90% of hepatocellular carcinoma cases occur after chronic liver disease. Cirrhosis of any cause is the main risk factor for HCC. In Asia and Africa, hepatitis B virus infection accounts for 60% of hepatocellular carcinoma cases, while in the West, it accounts for only 20%. Long-term heavy alcohol use can lead to hepatocellular cancer, cirrhosis, and alcoholic liver disease. Genome sequencing studies have identified several genes linked to hepatocellular carcinoma, although most genetic pathways involved are still unknown. There are three main surgical options for HCC: liver transplantation, tumor removal surgery, and tumor removal followed by additional therapy. Sorafenib is a multi-kinase inhibitor that blocks Raf-1 and other tyrosine kinases, which are essential for cell growth, differentiation, and survival. It is the first drug approved for systemic therapy and is the primary treatment for patients with advanced hepatocellular carcinoma who have preserved liver function and are not candidates for transplant or surgery.

Keywords: *Hepatocellular Carcinoma, Liver Neoplasm, Hepatitis D Virus, Nonalcoholic Steatohepatitis, and Surveillance Epidemiology and End Results.*

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I. INTRODUCTION

Hepatocellular carcinoma accounts for 75% of all primary and secondary liver cancer cases in the United States. The number of new cases and deaths is increasing, which is linked to geographical factors such as cirrhosis or chronic liver disease. Hepatocellular carcinomas (HCCs), originating from liver cells, make up about 80% of all liver cancers. In China, hepatocellular carcinoma is more common in people aged 55 to 59 than in North America and Europe, where the average age of diagnosis is between 63 and 65 years. Most cases of hepatocellular carcinoma occur in Southeast Asia, East Africa, and East Asia. The latest GLOBOCAN data show that more than 745,000 people died from liver cancer worldwide in 2012. The World Health Organization states that hepatocellular carcinoma is the second most common cause of cancer-related death. Its development results from a complex interaction between genetic and environmental factors. Liver cirrhosis, hepatitis B and C virus infections, excessive alcohol consumption, aflatoxin B1 exposure, and nonalcoholic steatohepatitis (NASH) all significantly influence HCC risk. The stage of the cancer at diagnosis impacts the prognosis for HCC patients.[1] Although it can take several months in advanced stages, early detection and effective treatment can lead to a five-year survival rate. Early diagnosis provides fewer and more effective treatment options. However, if the disease has spread and traditional chemotherapy is ineffective, the outlook is poor. Early treatment for hepatocellular carcinoma (HCC), including liver transplantation, local ablation, or surgical resection, improves survival chances. Therefore, prompt diagnosis and appropriate treatment are crucial for improving the quality of life and increasing survival rates in HCC patients. The Barcelona Clinic Liver Cancer (BCLC) staging system indicates that sorafenib enhances survival odds for patients with advanced stage C liver cancer, even if the disease has

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spread to blood vessels and the liver remains functional. Alpha-fetoprotein (AFP) has been used as a serum biomarker for detecting hepatocellular carcinoma. Unfortunately, AFP is not highly specific or sensitive, which limits its usefulness. A more accurate and reliable biomarker is needed for diagnosis. MicroRNAs, Glypican-3 (GPC 3), and Golgi 73 protein (GP 73) are some of the recent biomarkers identified in hepatocellular carcinoma. Advances in genetic research help us detect, predict, and treat HCC, and also reveal how molecular medicine may be used in future therapies. This review covers the latest information on hepatocellular carcinoma, including its causes, treatments, biomarkers, clinical features, and outcomes.[2]

- *Epidemiology*

Hepatocellular carcinoma is the fifth most common cancer worldwide and the second leading cause of cancer death. Hepatitis B and C viruses that persist in the body are the primary causes of hepatocellular cancer. The Surveillance Epidemiology and End Results (SEER) Database indicates that the incidence rate in the US increases by 3.1% annually. For men, the incidence is 11.5 per 100,000, while for women, it is only 3.9. The number of deaths from hepatocellular carcinoma each year has risen by 3.4% in women and 2.8% in men. Older individuals with chronic liver disease are more likely to develop hepatocellular carcinoma. Rates vary by race/ethnicity and location due to differing risk factors for exposure.[3] HBV is widespread globally, whereas HCV accounts for 30% of infections in the United States. The number of Americans born between 1945 and 1965 with HCV has increased fivefold, leading to a fivefold rise in liver cancer deaths. In 2018, liver cancer was the sixth most common cancer, with 841,080 new cases, and was the fourth leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma is more prevalent and deadly in East Asia and Africa, but is also increasing in some parts of the US and Europe. The Surveillance Epidemiology and End Results program reports that in the early 2000s, hepatocellular carcinoma was the leading cause of cancer deaths in the US. If current trends continue, it is projected to become the third leading cause of cancer deaths by 2030.[4]

- *Risk Factors and Causes*

Chronic liver disease occurs before around 90% of occurrences of hepatocellular carcinoma. Cirrhosis of any cause is the main cause of hepatocellular cancer. Hepatocellular carcinoma (HCC) is the main reason people with cirrhosis die. It happens between 1% and 6% of the time each year. Chronic alcohol consumption, diabetes, being overweight, and having hepatitis B or C viruses can all raise the risk of HCC. Other, less common causes include hemochromatosis, α1-antitrypsin deficiency, and cirrhosis caused by primary biliary cholangitis. People with cirrhosis caused by hemochromatosis are more likely to get hepatocellular carcinoma. Up to 45% of these persons may get HCC throughout their lifetime.[5]

- *The Hepatitis B Viral Infection*

Hepatitis B virus infection causes 60% of hepatocellular carcinoma cases in Asia and Africa, but only 20% of cases in the West. The Hepatitis B virus is a DNA virus that may get into host genomes and cause insertional mutagenesis and the activation of oncogenes. Most people with HBV-induced hepatocellular carcinoma (HCC) also have cirrhosis. However, HBV increases the risk of HCC even in those who do not have cirrhosis.[6] Because the risk of hepatocellular carcinoma is higher than the cost-effectiveness criteria for men over 40 and women over 50, monitoring programs are very important in East Asia, where endemic hepatitis B virus infection is quite common. Aflatoxin B1, together with HBV, raises the risk of HCC and is probably to blame for the higher rates of HCC in African individuals in their 30s and 40s. Most Asian countries have not yet set up universal vaccination programs; however, certain areas have successfully lowered the number of HCC cases by using HBV vaccine techniques.[7]

- *The Hepatitis C Viral Infection*

Chronic hepatitis C virus (HCV) infection is a common liver disease that comes before hepatocellular carcinoma in people in the United States, the European Union, and Japan. Cirrhosis and chronic liver injury with bridging fibrosis are the main risk factors for hepatocellular carcinoma linked to HCV, an RNA virus that does not become part of the host genome. This is not true for HBV. Direct-acting antiviral (DAA) drugs have helped more and more people with HCV get a sustained virologic response (SVR), which lowers their risk of hepatocellular carcinoma by 50–80%. Many of these patients have not been tested for HCV and do not know they are infected, especially among racial and ethnic minorities and those living in low-income areas. People with HCV-induced cirrhosis also need close monitoring since their risk of getting HCC (>2% per year) is high even after they reach SVR.[8]

- *The Hepatitis D Viral Infection*

Certain surface antigens are needed for the hepatitis D virus (HDV) to grow and spread. Because HDV affects 20 to 40 million people throughout the world, liver fibrosis and cirrhosis are more common in people with HDV than in those with HBV alone. Other cohort studies have also shown that having both HDV and HBV increases the risk of HCC compared to having just HBV. A big research study found that both acute HDV infection (RR 6.1, 95% CI 2.8–11.7) and chronic HDV infection (RR 3.9, 95% CI 1.6–7.2) are connected to a much higher risk of HCC than HBV infection alone.[9]

- *Alcohol*

Long-term heavy drinking can lead to cirrhosis, hepatocellular cancer, and alcoholic liver disease. More and more people are getting cirrhosis because of non-alcoholic steatohepatitis. Alcohol-related cirrhosis is responsible for about 15–30% of hepatocellular carcinoma cases. The yearly rate of new cases ranges from 1% in population-based studies to 2–3% in tertiary care referral centres. Chronic alcohol use may increase the risk of hepatocellular carcinoma (HCC) from many different causes. For example, studies have shown that people with hepatitis B virus (HBV) who drink alcohol are more likely to have HCC than people who don't drink. Data shows that people go through alcohol-specific pro-

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tumorigenic pathways, even while drinking alcohol is linked to several disease processes in cirrhosis, such as NASH.[10]

➢ *Nash*

Non-alcoholic steatohepatitis is a common cause of cirrhosis in people who are obese or have diabetes. NASH is the first stage of hepatocellular carcinoma's growth. Nonalcoholic steatohepatitis is becoming the most common cause of cirrhosis across the world since obesity is becoming more common. Since 2010, the number of hepatocellular carcinoma diagnoses attributable to NASH has gone up a lot in Western nations.[11] It now makes up 15-25% of all cases. Also, the percentage of both illnesses that can be linked to the population is projected to be more than 20% because metabolic syndrome and NASH often happen together in people with other liver problems. Cirrhosis caused by non-alcoholic steatohepatitis (NASH) has a lower yearly incidence of hepatocellular carcinoma (1-2%) than cirrhosis caused by viruses (3-5%). However, it is still over 1.1 per 100 person-years, which means that it has to be watched closely. New research shows that monitoring strategies that only look at cirrhotic patients are not enough, since 25-30% of hepatocellular carcinoma linked with non-alcoholic steatohepatitis (NASH) occurs in people who do not have cirrhosis. A cohort study from the National Veterans Affairs health system showed that monitoring is not needed since the yearly rate of HCC in non-cirrhotic NASH patients is below the cost-effectiveness threshold.[12]

➢ *Gender, Age, and Additional Factors*

Patients with cirrhosis who have hepatocellular carcinoma tend to have certain sociodemographic traits. People over 70 had the greatest age-specific incidence, which means that becoming older is a big risk factor. The reason that males are more likely to have HCC than women (2:3:1) may be due to differences in sex hormones and a larger number of risk factors among men. Research shows that Hispanics and other racial or ethnic minorities are more likely to have HCC than white people.[13] The higher number of single-nucleotide mutations in PNPLA3, which are connected to NASH-related HCC, may explain this disparity. Epidemiological studies show that smoking increases the risk of developing hepatocellular carcinoma. Studies show that coffee and aspirin may help lower the risk of HCC, although it's still not clear how diet affects this risk.[14]

➢ *Pathophysiology*

Genome sequencing research has found a number of genes that are linked to hepatocellular carcinoma; however, most of the genetic pathways that cause the disease are still not known. Genomic instability, which shows up as single-nucleotide polymorphisms or chromosomal abnormalities, may help liver cancer cells grow. Specific signalling pathways that are linked to repeated changes in somatic genes are a major cause of hepatocellular carcinoma. Some of these genes are TP53, CTNNB1, ARID1A, FGF, and the TERT promoter. There is still no clear cause or specific treatment for hepatocellular carcinoma since it has a lot of different genetic types. Changes in the TP53 gene and the synthesis of the Ki-67 protein are known to be prognostic indicators for this cancer, and they are often connected to a poor prognosis. The main problem with younger patients is figuring out the difference between fibrolamellar variation and tumour encapsulation. These lesions are easier to remove, less likely to be linked to cirrhosis or viral infections, have normal AFP levels, and usually have a better prognosis than classical hepatocellular carcinoma, which mostly affects older people with chronic conditions and is only possible to remove in less than 25% of cases. [15]

II. CURRENT THERAPIES AND THEIR LIMITATIONS

Several treatments for hepatocellular carcinoma rely heavily on apoptosis, the cell cycle, and changes in signalling pathways. The next section explains the many types of therapy.[14,15]

➢ *Pharmacological Therapy*

Sorafenib is a multi-kinase inhibitor that stops Raf-1 and other tyrosine kinases from working. These kinases are important for cell growth, differentiation, and survival. This is the first drug licensed for systemic treatment. It is the main treatment for those with advanced hepatocellular carcinoma, retained liver function, and who can't have a liver transplant or surgery to remove the cancer. The results show that fixing the wrong glycosylation in the erythroblastosis 26-1 (Ets-1) protein in HCC cells is linked to higher survival rates in patients with advanced HCC who have been treated with sorafenib. Some people quickly become resistant to sorafenib. Lenvatinib is a good therapy for individuals with hepatocellular carcinoma who are resistant to sorafenib and don't respond to surgery. It works by stopping lymphangiogenesis and angiogenesis. The FDA approved regorafenib, a second-line oral medication made by Bayer, for unresectable HCC in June 2017. Ramucirumab is a human monoclonal antibody that blocks the binding of VEGFR ligands. Medications like sorafenib and lenvatinib can cause side effects including high blood pressure, diarrhoea, and loss of appetite; however, drug resistance is still a big problem for many medications.[16]

➢ *Surgery*

For people with hepatocellular carcinoma (HCC), the three main types of surgery are liver transplantation, adjuvant treatment after resection, and surgical resection. People with maintained liver function who have hepatocellular carcinoma should have surgery to remove the cancer. Laparoscopic liver resection has benefits including shorter hospital stays, faster recovery times, and less blood loss. After surgery, individuals with early hepatocellular carcinoma (≤5 cm) with liver function that is still good may have a 40–70% chance of surviving for five years. After surgery, problems with recurrence can be resolved by further hepatectomy, radiofrequency ablation, or salvage liver transplantation. After surgery, adjuvant treatment gets rid of any remaining cancer cells and stops liver cancer from coming back. Interferons, intra-arterial and systemic chemotherapy, sorafenib, acyclic retinoid, adoptive immunotherapy, and intra-arterial radiolabeled lipiodol are all treatments that can be used. People with moderate to severe cirrhosis or early-stage hepatocellular carcinoma should get a liver transplant.

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It also lowers the risk of liver failure after surgery. Liver transplantation has a better 10-year survival rate than liver resection, but it also has risks, such as donor liver rejection and high expenses, which might lead to death that wasn't planned.[17]

- *Loco-Regional Therapy*

Radiofrequency ablation, ethanol injection, and cryotherapy are all types of loco-regional ablative treatment. This drug will either help people with HCC who can't have surgery live longer without the illness or help them get a liver transplant. Percutaneous ethanol injection (PEI) is the standard ablative treatment for people with early-stage hepatocellular carcinoma (HCC). However, radiofrequency ablation (RFA), which uses coagulative necrosis to kill HCC cells with heat, works far better. Also, RFA greatly lowers the risk of complications in those with moderate HCC compared to liver resection.[18]

- *Cytotoxic Chemotherapy*

People with liver problems other than cirrhosis are more likely to respond well to chemotherapy. People with advanced HCC can't get standard chemotherapy since the tumour is naturally resistant to it. People who already have liver disease can't have systemic chemotherapy. There are additional chemotherapy options. For example, using doxorubicin at a dosage of 75 mg/m2 results in an objective response rate of 20% or lower in patients with advanced HCC. When treating HCC, systemic chemotherapy doesn't work very well, is quite toxic, and doesn't improve survival rates compared to regimens that include gemcitabine and doxorubicin.[11,18]

- *Natural Compounds*

Fruits, vegetables, and spices all have different natural components that may stop cancer from spreading and make cancer-prevention methods work better. These molecules help the body fight against cancers, free radicals, inflammation, and cell growth. Some drugs kill cancer cells but leave healthy cells alone. In the future, natural compounds like piperine may be used alongside chemotherapy to raise plasma levels by stopping enzymes that break down drugs. Allium extracts, curcumin, oleocanthal, and Cnidium officinale Makino are all natural substances that are used to stop hepatocellular carcinoma (HCC) from getting worse. Natural substances can protect the host from damage and make existing drug therapies work better. Polysaccharides from Lentinus edodes and Tricholoma matsutake make 5-fluorouracil work better against H22 cells isolated from people with hepatocellular cancer.[17,19]

- *Oncolytic Virus Therapy*

Oncolytic viral therapy is a new way to treat cancer that kills tumour cells by making viruses that kill cancer cells in cancerous tissues. These anticancer drugs only work on tumours and have several ways of killing cancer cells. They do this by directly targeting cancer cells with proteins generated by transgenes and showing pleiotropic cytotoxic immune effector functions. Adenovirus, parvovirus, herpes simplex virus, reovirus, and paramyxovirus are just a few of the viruses that are involved in this process. Scientists have changed the genes of many viruses to make them more useful as medicines. Oncolytic viruses not only change the pathways that make cells resistant to tumours, but they also make cancer cell lysates that help find new tumour antigens and cause tumour cells to die in a way that makes them immune. The adenoviral E1A promoter was replaced by the telomerase reverse transcriptase promoter that is specific to tumours. This change made it possible for oncolytic viruses like competent oncolytic adenovirus, telomerase-specific replication, and telomelysin (OBP-301) to replicate well in telomerase-positive cancer cells in hepatocellular carcinoma.[18,19]

- *Immunotherapy*

Immunotherapy for HCC tries to boost the body's natural immune response against cancer cells. This plan calls for giving patients with metastatic melanoma antibodies that block immunological checkpoint pathways, such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4). Activated T and B cells control peripheral immunological tolerance through the co-inhibitory receptor programmed death 1 (PD-1). The interaction between PD-1 and its ligands, such as programmed death ligand 1 (PD-L1) (B7-H1) and PD-L2 (B7-DC), is an important part of the immune system that keeps it from working too hard. Cytotoxic T lymphocytes (CTLs) may boost the immune system by identifying tumor-associated antigens (TAAs). HCC cancers have a lot of squamous cell malignant antigens, namely TAA, cyclophilin B, AFP, hTERT, GPC3, and MAGE-A. Sorafenib reduces immunosuppression, which means it can be used with other immunotherapeutic drugs at the same time.[16, 20]

- *Nanotechnology*

Nanotechnology is changing the way standard combo therapy works by making drugs stay in the body longer and easier to get through. The nanoparticle technique blends several medications into a uniform therapy regimen to maximise their efficacy. When incorporated, nanoparticles increase outcomes by injecting an alternative chemical into the process, which is particularly useful for tackling drug-resistant chemosensitized cancer cells. Following 48 hours of doxorubicin treatment with lipid nanoparticles as chemo-sensitizers delivered to HepG2 cells, the cytotoxicity was lowered compared to free doxorubicin and doxorubicin-nanoparticles, indicating possible synergy. In contrast to free doxorubicin and curcumin, the synergistic combination of doxorubicin and curcumin significantly suppresses the growth of liver tumours produced by diethylnitrosamine.[17, 18, 20]

III. CONCLUSION

Hepatocellular carcinoma, a sort of primary liver cancer, is a deadly sickness usually connected to liver cirrhosis, hepatitis B and C infections, heavy alcohol consumption, and genetic predispositions. Liver transplantation, adjuvant therapy, surgical resection, and multi-kinase inhibitors like sorafenib are all common treatments for advanced hepatocellular carcinoma. Sorafenib, lenvatinib, and regorafenib are all effective treatments for advanced

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hepatocellular carcinoma. However, liver transplantation and surgical resection are still necessary to keep the liver working properly. Natural medications like curcumin and oncolytic virus therapy may improve existing treatments. However, loco-regional therapies like radiofrequency ablation are good for those with early-stage hepatocellular carcinoma. Nanotechnology and immunotherapy are new ways to improve the outcomes of treatment for people with hepatocellular carcinoma.

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