Review Article

A Global Review of Hepatocellular Carcinoma (HCC)

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ABSTRACT

Hepatocellular carcinoma is the leading cause of death in cirrhosis. Hepatocellular carcinoma is the sixth most prevalent cancer and the third most frequent cause of cancer-related death. To review the risk factors, causes, morphology, enzymatic pathways and management strategies involved in hepatocellular carcinoma. A literature search was performed using PubMed for publications with a predetermined search string to identify relevant studies. The diagnosis and treatment schedule used for the successful management of hepatocellular carcinoma. Studies combining sorafenib with locoregional or other targeted molecular therapies are likely to improve responses and outcome.

Keywords: Hepatocellular carcinoma, Cirrhosis, Liver transplantation, Hepatitis B and Hepatitis C.

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INTRODUCTION

HEPATOCELLULAR CARCINOMA (**HCC**) is the most common type of primary liver cancer in adults, and is the most common cause of death in people with cirrhosis[1]. Hepatocellular carcinoma is the sixth most prevalent cancer and the third most frequent cause of cancer-related death.[2,3]

History of Hepatocellular carcinoma

The history of Hepatocellular carcinoma is very difficult to outline, because it depends on a series of variables that, when combined, can evolve into the disease, not only in different subjects, but also sometimes within the same subject. The number and size of neoplastic nodules at diagnosis, the growth speed pattern of the nodule(s), and the severity of the underlying liver disease. Currently, with improvement in diagnostic tools (ultrasound, helicoidal CT), HCC is more often found as one nodule or nodules of small size, allowing patients to be treated radically. The doubling time of a nodule of small dimensions has been estimated within a period of 1–19 months, thus indicating the great variability, and there are some small nodules that after an extended period of stability can grow rapidly. On the contrary, some nodules with initial fast growth can subsequently stop growing. Nodules with fast initial growth are those that nullify attempts to screen for HCC in patients with liver cirrhosis, because within a time lapse of 6 months ultrasound can reveal a neoplastic liver that has developed beyond the bounds of radical treatment. The discovery of a neoplastic nodule in Child's class C patients doesn't modify the explanation of liver cirrhosis, and for this reason these patients are excluded from screening programs. Untreated patients with HCC in Child's class A or B, who are historical or belong to the control arm of randomized controlled trials, have a different prognosis, which is better in those patients with better underlying hepatic function. Another variable that seems to affect the survival of patients with unresectable liver neoplasia is the state of the estrogen receptor on the surface of the hepatocytes. Patients with the wild-type estrogen receptor live longer than do patients with a variant form of estrogen receptor on the hepatocyte surface.[4]

EPIDEMIOLOGY OF HCC

The hepatocellular carcinoma (HCC) has led to the clear identification of several risk factors. These include chronic infection with hepatitis B and/or hepatitis C and exposure to aflotoxin. All these agents may cause hepatocellular carcinoma but how they interact and how they are related to cirrhosis, which underlies most cases, remains an area of active research. Intervention programmes, most notably immunization against hepatitis b, are now under way and a marked decrease in incidence of hepatocellular carcinoma can be anticipated in the early part of the next century.[5]

Morphology of Hepatocellular carcinoma

In macroscopic forms HCC grows in three forms:

Nodular (multifocal), Massive (unifocal) and Diffusely infiltrative.

In microscopic pattern has divided into four major types:

Trabecular, Pseudoglandular, Solid and Scirrhous.[5]

CAUSES

The following things that may increase your risk for getting HCC

Viral Hepatitis B and Hepatitis C

Hepatitis B and Hepatitis C: Both are passed through blood, such as when drug users share needles. Blood tests can show whether you have infected with hepatitis B or C. Hepatocellular carcinoma can develope after a year's you've had one of these liver infections.

Liver Cirrhosis

Main cause of liver cirrhosis is frequent consumption of alcohol. This serious disease happens when liver cells are damaged and replaced with scar tissue.so many reasons led to cause a cirrhosis i.e., hepatitis B or C infection, alcohol drinking, certain drugs, and large quantity of iron storage in liver.

Heavy alcohol consumption

Having more alcoholic drinks for many years raises your risk of hepatocellular cancer. The more you drink, the higher your risk.

Obesity and Diabetes mellitus

Obesity and diabetes Both conditions raise your risk of liver carcinoma. Obesity can lead to non-alcoholic fatty liver disease, which can lead to hepatocellular carcinoma or liver cancer. Higher risk from diabetes may be due to liver damage caused by the disease. Plus, people with diabetes are often overweight or obese.

Anabolic steroids

Anabolic Steroids are the drugs which mimic the male sex hormone testosterone, steroids are used by athletes to build muscle mass**.** Long-term use of steroidal drugs can increase your risk.

Iron storage disease

This causes too much iron to be stored in the liver and other organs. It may lead to develop hepatocellular carcinoma.

Aflatoxin

Aflatoxin is a harmful substance, which is made by certain types of mold on peanuts, corn, and other nuts and grains, can cause HCC. In U.S. food safety teams has measures limit aflatoxin in the food supply.[6]

RISK FACTORS

The Risk factors of HCC are well documented, the synergisms between these risk factors are not well examined. The basic information about risk factor was collected by the Blood samples, were tested for the presence of antibodies to hepatitis C virus antigen (anti-HCV), Hepatitis B surface antigen (HBsAg), and antibodies to hepatitis B core antigen (anti-HBc), heavy alcohol consumption, and diabetes mellitus, respectively. Most common risk factor of HCC is hepatitis viral infections, heavy alcohol consumption and diabetes mellitus.[6]

Role of viral hepatitis C virus in HCC

The patients with HCC more than 70% of people have anti-HCV antibody in the serum. Mostly cirrhotic liver patient has reported as neoplastic degeneration, whereas only a few cases of HCV-associated HCC have been reported in the noncirrhotic liver. The time lapse for the development of HCC in patients infected with HCV is much longer and includes all intermediate steps from mild chronic hepatitis, to severe chronic hepatitis, to liver cirrhosis, and finally to HCC. The risk of developing HCC becomes more significant in subjects with liver cirrhosis

Role of viral Hepatitis B virus in HCC

The studies associate HBV, as well as HCV, with the development of HCC. The incidence of developing HCC, like that for the HCV, is conditioned by the presence and severity of the underlying liver disease.

Role of aflatoxin B1 in HCC

Aflatoxin B1 has long been associated with the development of HCC, because areas with a large consumption of this toxin coincide with areas with a high incidence of HCC. It is produced by a fungus of the genus Aspergillus. The fungus represents a common contaminant of foods (corn, grain, legumes, peanuts etc.), producing large quantities of toxin. However, it was recently observed that areas that have a high incidence of HCC and high aflatoxin intake correspond to areas in which HBV infection is endemic and that patients at higher risk of developing HCC are those who are exposed to both HBV and AFB1 risk factors. A case control study using biomarkers of exposure to AFB1, such as urinary metabolites of AFB1 (or) the blood concentration of AFB1, did not confirm the responsibility of AFB1 in the development of HCC, for this reason it has been proposed that in addition to a high intake of AFB1, patients who previously were exposed to HBV should be considered at higher risk of developing HCC.

Role of alcohol

Alcohol is directly responsible for neoplastic degeneration. but it has not been proved experimentally to be mutagenic. Alcohol is most common etiologic agent of liver cirrhosis, through which it can tendency to the development of HCC. Whatever the etiology of cirrhosis, once it has been diagnosed, it is the main cause of neoplastic degeneration of the liver. However, high alcohol intake over a long period (at least 5 years) is necessary for the development of liver cirrhosis. Low or moderate intake of alcohol is not associated with the development of liver cirrhosis and consequently of HCC.[4]

SYMPTOMS OF HCC

- Pain occurs in the upper right part of your belly
- A feeling of heaviness in your upper belly

- Bloating or swelling in your belly
- Loss of appetite and feelings of fullness
- Loss of weight
- Weakness or deep fatigue
- Nausea and vomiting
- Yellow skin
- Yellow eyes
- Pale, chalky bowel movements and dark urine
- Fever[8]

THE DEVELOPMENT OF HEPATOCELLULAR CANCER IN HUMANS

Integration of hepatitis B virus DNA probably acts as a genotoxic initiator in the multistep process of hepatocarcinogenesis, although the accurate mechanisms involved in the carcinogenesis is not been determined.Aflatoxin intake can also have an etiological role in high incidence regions, probably as a genotoxic or epigenetic promoter to hepatitis B virus-initiated carcinogenesis.In low risk populations cirrhosis is that the most vital causal association of hepatocellular cancer. The condition of cirhosis developed in the result of alcohol abuse, but the tumour may complicate all etiological forms of this disease.Whether neoplasia is an inevitable consequence of the hyperplasia of cirrhosis, or the increased hepatocyte employee turnover acts as a promoter isn't known.Hepatitis B viral infection plays a lesser part, and aflatoxin no part in the least.[9]

ENZYMATIC PATHWAYS, GROWTH FACTORS AND ANGIOGENIC PROCESSES INVOLVED IN HEPATOCARCINOGENESIS

Cellular signaling pathways involved in HCC. Several signaling pathways have been shown to be a major role in HCC. These pathways differ in different settings, because a variety of risk factors cause HCC, each in their own unique manner[10].Major intracellular enzymatic pathways are involved in the process of hepatocancerogenesis; and the enzymatic cascade activated by the binding of epidermal growth factor (EGF) to its receptor[11]

1. Wnt/ ß-catenin (Aflatoxin, Alcohol HBV, HCV)
2. Jak/STAT
3. pRB(HBV)
4. MAP kinase (HBV, HCV)
5. Stress
6. Inflammation/ cytokines
7. Growth factors (EGF/TGF-ß)
8. p53 (Aflatoxin,HBV)
9. Hemachromatosis (HBV HBV, HCV A)[12]

DIAGNOSTIC METHODS OF HEPATOCELLULAR CARCINOMA

1. Microarrays[13]
2. quantitative real-time PCR[13]
3. CT scan[14]
4. MRI[14]
5. Confirmation by liver biopsy[14]

To find such biomarkers, we studied microRNA expression in 144 tumor samples using custom microarrays. Hsa-miR-141 and hsa-miR-200c, microRNAs that promote epithelial phenotypes, had significantly higher levels in non-hepatic epithelial tumors. In contrast, endothelial-associated hsa-miR-126 showed higher expression levels in hepatocellular carcinomas. Combinations of those microRNAs accurately identified primary hepatoma from metastatic adenocarcinoma within the liver. These findings were validated using quantitative real-time PCR to measure microRNA expression in additional samples. Thus, the tissue-specific expression patterns of microRNAs make them useful biomarkers for the diagnosis of liver malignancies[13]. Diagnostic tools commonly used include the serum tumor marker alfa-fetoprotein (AFP), radiographic imaging, and liver biopsy.[15] The use of triphasic computerized tomography scanning and improved resonance imaging equipment and protocols has led to greater sensitivity and specificity for these techniques in diagnosis of hepatocellular carcinoma[15]

Liver transplantation has grown in importance as a treatment for hepatoma but could also be limited by availability of donor organs and long waiting times. This situation could also be improved by greater use of living donor liver transplantation. Hepatic resection remains a crucial treatment modality for hepatoma, particularly within the absence of cirrhosis. Tumor ablation by alcohol injection or radiofrequency ablation is related to favorable outcomes and should be considered a potentially curative treatment. Early diagnosis of hepatoma remains a key goal in improving the poor prognosis of this type of cancer of the liver. Identifying hepatoma at an early stage is usually related to having better treatment options for patients with small, asymptomatic tumors.[15]

IMMUNO HISTOCHEMCAL ANALYSIS

Immunohistochemical analysis of hepatocellular carcinoma plays an important role in practical diagnosis. Metastatic tumors of the liver (breast, pancreas, kidney and adrenal gland cancers) are more common than primary ones. In routine histological examination they may imitate primary hepatic cancer. Precise diagnosis is of vital importance for therapy and prognosis.[6]

THERAPY OF HCC

Hepatocellular carcinoma therapy include:

Surgery

Surgery to remove the carcinoma and a margin of healthy tissue that surrounds it may be an option for people with early-stage liver cancers who have normal liver function.

Liver transplantation

Surgery to remove the entire liver and replace it with a fresh liver from a donor may be an option in otherwise healthy people whose liver cancer hasn't spread beyond the liver.

Destroying cancer cells with heat or cold

Ablation procedures to kill the cancer cells in the liver using extreme heat or cold may be recommended for people who can't undergo surgery. These procedures include radiofrequency ablation, cryoablation, and ablation using alcohol or microwaves.

Delivering chemotherapy to cancer cells

Using a catheter that's passed through your blood vessels and into your liver, doctors can deliver chemotherapy drugs (chemoembolization) or tiny glass spheres containing radiation (radioembolization) directly to the cancer cells.

Radiation therapy

Radiation therapy using energy from X-rays or protons may be recommended if surgery isn't an option. A specialized type of radiation therapy, called stereotactic body radiotherapy (SBRT), involves focusing many beams of radiation simultaneously at one point in your body.

Targeted drug therapy

Targeted drugs attack specific weaknesses in the cancer cells, and they may help slow the progression of the disease in people with advanced liver cancers.

Immunotherapy

Immunotherapy drugs use your body's germ-fighting immune system to attack the cancer cells. Immunotherapy may be an option for treating advanced liver cancer.

Clinical trials

Clinical trials give you a chance to try new liver cancer treatments. Ask your doctor whether you're eligible to participate in a clinical trial.[16]

Drug treatment for Hepatocellular Carcinoma

STAGE 0 → patient with very early HCC → Resection

STAGE A → Patient with early HCC → Resection, liver transplantation

STAGE B → Patient with immediate HCC → Transarterial chemoembolization (TACE)

STAGE C→Extrahepatic spread or cancer related symptoms→Sorafenib

STAGE D→End stage disease→symptomatic treatment[17]

CONCLUSION

Early diagnosis and definitive treatment remain the key to long-term outcome. A multidisciplinary approach is critical to the successful management of hepatocellular carcinoma. Studies combining sorafenib with locoregional or other targeted molecular therapies are likely to improve responses and outcome.

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