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Emerging Therapies in Hepatic Carcinoma: A Review

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Abstract

The most common primary liver cancer, hepatocellular carcinoma, or HCC, is responsible for the vast majority of cancer-related deaths worldwide. In the United States, HCC is the seventh most prevalent cause of cancer mortality. Despite breakthroughs in prevention, screening, and new technology for diagnosis and treatment, the incidence and fatality rates continue to climb. Whatever the reason, the greatest threat for developing HCC is still cirrhosis.. Hepatitis B and C are substantial risk factors for developing cirrhosis. Alcohol intake is an important risk factor in the United States, with alcohol abuse five times greater than hepatitis C. The diagnosis is verified without pathologic confirmation.

At 6-month intervals, screening includes radiologic tests including ultrasound, computed tomography, magnetic resonance imaging, and serological indicators like -fetoprotein. There is several therapy options available, but only orthotopic liver transplantation (OLT) or surgical excision is effective.

Carcinoma size, location, extrahepatic dissemination, and intrinsic liver function are taken into consideration while selecting a treatment approach. Hepatocellular carcinoma (HCC) is an aggressive cancer that often develops in advanced stages alongside cirrhosis. To prevent HCC measures such as hepatitis B virus vaccination, blood product screening, safe injection practices, treatment for alcoholics and intravenous drug users, and antiviral therapy should be implemented. Continuous improvement in both operational and therapeutic approaches has significantly increased overall survival.

Keywords: Hepatocellular Carcinoma; Hepatitis; Treatment; Metastasis

Abbreviations

OLT: Orthotopic Liver Transplantation; HCC: Hepatocellular Carcinoma; MS: metabolic syndrome; HGV: Hepatitis G Virus, TTV: Transfusion-Transmitted Virus; AFM1: Aflatoxin Metabolite M1; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; TGF-Alpha: Transforming Growth Factor Alpha; US: Ultrasonography; CT: Multiphase Computed Tomography; MRI: Magnetic Resonance Imaging; OLT: Organ Transplantation; PEI: Percutaneous Ethanol Infusion; RCTs: Randomized Controlled Trials; 5-FU: 5-Fluorouracil; TACE: Trans Arterial Chemoembolization; BMI: Body Mass Index; HBsAg: Hepatitis B Surface Antigen; BLCL: Burkitt Lymphoma Cell Line.

Introduction

Liver cancer is a global health issue, with liver neoplasms being the second most common cause of cancer-related mortality in 2012. The incidence rate has lately risen, with

estimates fluctuating between 1.9 to 4.3 cases/100,000 men and 0.8 to 13.9 cases/100,000 females [1]. The high incidence and fatality rates have resulted in a tremendous financial burden on families and society for medical care and insurance, frequently leading to crises. Notably, hepatocellular tumor (HCC), the most frequent kind of liver cancer, is believed to account for 70% to 90% of all primary liver tumors. Numerous studies have identified risk factors for hepatocellular carcinoma (HCC), such as alcohol abuse, metabolic syndrome (MS), nonalcoholic fatty liver disease, hepatitis B and hepatitis C virus infections, and chronic liver cirrhosis [2].

Clinical breakthroughs have mostly occurred in imaging for medical surgery, regional cancer treatment, and biotherapy. Rapidly expanding information in fundamental research emerges at the molecular level, notably in investigating HCC invasiveness. Despite significant advancements in HCC treatment, patients' outcomes remain poor. In the United States, the relative 5-year survival rate for liver cancer climbed from 4% (1974-76) to 6% (1986-93) for whites and from 1% to 4% for blacks. In Shanghai, the 5-year survival rate for liver cancer was 4% between 1988 and 1991. These findings suggest that overcoming HCC remains a significant challenge.

The primary causes of HCC are widely understood. Diabetes mellitus and an increased BMI, particularly in males, are well-known risk factors. Some of the stages involved in the molecular pathogenesis of HCC have been identified in recent years. Hepatocarcinogenesis, like most other kinds of cancer, is a multistep process involving several genetic changes that eventually lead to the transformation into cancer of hepatocytes. Although colorectal cancer and certain blood-forming malignancies have made significant progress in understanding a chain of events, the molecular contribution of multiple factors and their interactions in hepatic-carcinogenesis remains unclear.

Causes

Aflatoxin, Alcohol, and Viral Infections Such as Hepatitis B and C (HCV) are the Primary Triggers for HCC: However, the relative impact of these many elements varies by geography. HBV is more prevalent in HCC patients from China, Southeast Asia, and Africa, whereas HCV is frequent in HCC patients from industrialized nations (Japan, France, Italy, and others) [3]. In China, the prevalence of hepatitis B (HBsAg) surface antigen and HCV antibody (anti-HCV) in HCC patients was 63.2% and 11.2%, respectively [4,5]. This is consistent with previous reports. Prospective studies indicate a supplement effect of HCV and HBV infection on HCC development [6]. Cirrhotic individuals infected with HCV type 1b are substantially more likely to develop HCC than patients infected with other HCV types [7].

Hepatitis G virus (HGV) and Transfusion-Transmitted Virus (TTV) Infection may not Play a Significant Influence: Based on evidence from China, Japan, Africa, the UK, and other sources, HGV may not have an essential role in forming HCC. Case-control research also found no evidence to support the concept that transfusion-transmitted virus (TTV) transmission is associated with HCC. However, several scientists argued that HGV and TTV could not be entirely ruled out as causal factors. In China, HBV and HCV (mostly HBV), aflatoxin, and water pollution (such as microcystin, a hepatocarcinogen) continue to be key risk factors for HCC, and drinking should be included in northern China. A study found that exposure to the aflatoxin metabolite M1 (AFM1) might account for a significant percentage [8].

Other Risk Factors Were Also Noted: In Japan, alcohol use and smoking cigarettes were both risk factors for HCC, and a synergistic effect was observed. In Italy, excessive alcohol consumption had the highest risk factor (AR) of HCC (45%), followed by HCV (36%), and HBV (22%). The risk of dietary iron excess for HCC in black Africans was 4.1, which is comparable to the risk of hemochromatosis in Caucasians. Family history was also shown to have a role in HCC, both alone and in conjunction with recognized risk factors, with an odds ratio of 2.4 [9].

The HBV X protein is one of the targets for how HBV promotes HCC.

The prevalence of HCC in transgenic mice harboring HBV-X was as high as 86%. The structure of the X gene was also discovered to be altered in the majority of tumorous livers, indicating that mutant X proteins may play a role in HBV-related liver oncogenesis. Furthermore, HBV-X may contribute to hepatic inflammation by increasing interleukin-6 creation, which can eventually lead to HCC. HBV preS1 transactivated the transforming growth factor alpha (TGF-alpha) gene, offering insight into viral hepatocarcinogenesis. It was also discovered that TGF-alpha and HBsAg work together to promote hepatocellular growth and carcinogenesis [10].

Screening

Improving patient outcomes and reducing mortality should be the main objectives of HCC surveillance. Early screening for HCC has been linked to improved patient survival, according to studies. Early diagnosis gives patients a variety of treatment alternatives, which improves their results [11,12]. Since surveillance for the broader public is not advised, defining the target audience should be a top concern in light of today's spiraling healthcare expenses [13]. Clinical effectiveness is defined as a minimum 100-day improvement

in lifespan following an intervention (screening method). An intervention would be deemed cost-effective if it resulted in a life gain of less than $50,000 annually [14].

Monitoring intervals for HCC is based on the usual tumor growth time of three to five months and an economical threshold of an expected annual incidence exceeding 1.5% in fibrosis patients and 0.2 percent in non-cirrhosis individuals with hepatitis B. Considering these parameters, screening for HCC should be performed on every patient with cirrhosis; however, screening in cases of primary biliary cirrhosis and autoimmune hepatitis cirrhosis may not be as beneficial [15]. Patients with severe or decompensated liver failure who are not candidates for transplantation may also be an exception to this rule. They have very little time left to benefit from monitoring in terms of survival.

Females >50 years	Males > 40 years
Africans >20 years	Family Background of HCC
Non-Asian female > 50 years	Non-Asian Black male > 40 years

Table 1: Screening of HCC.

Methods of Screening

Radiographic testing and serological marker screening are two of the several modalities for HCC screening. Ultrasonography (US), multiphase computed tomography (CT), and magnetic resonance imaging (MRI) with contrast are popular radiological techniques used for surveillance. Since the early 1980s, the US has been used historically to diagnose intrahepatic lesions [16]. Studies have shown that when US imaging is utilized for screening, its specificity may reach >90%. The sensitivity of this type of imaging can vary, ranging from 35% to 84%, depending on the operator and equipment. A total of 85% of tumors that were not picked up by the US had little HCC nodules measuring less than 2 cm. Moreover, central obesity makes it more difficult for ultrasonography to identify tiny lesions [17].

Moreover, central obesity makes it more difficult for ultrasonography to identify tiny lesions. On both CT and MRI images, HCC lesions show reduced contrast agent presence during the portal phase of imaging (washout) and increased arterialization. CT and MRI have a 90% sensitivity for detecting cancers larger than 2 cm, 90% sensitivity for tumors between 1 and 2 cm, and 65% and 80%–92% for tumors less than 1 cm, respectively [18]. When using Ultrasonography as the initial modality when the patient's findings are ambiguous, CT and MRI are recommended.

AFP's primary role is to regulate fatty acids in fetal and growing adult liver cells. AFP has been utilized as the plasma marker for HCC identification since 1968. According to many studies, AFP has a sensitivity of 21%-64% and a specificity of 82%-93% [19]. One significant drawback is that levels of AFP may be mistakenly elevated in individuals who have ongoing hepatitis but no signs of HCC. The commonly accepted greater limit of normal is 20ng/mL, as AFP levels among healthy people seldom reach this amount. In 16% of chronic hepatitis C individuals without HCC, AFP levels exceed 20ng/mL [18-22].

Diagnosis

Early diagnosis is crucial for optimal HCC treatment outcomes. Chronic hepatitis causes the development of cirrhosis. Establishing clusters in the liver are a result of hepatocyte proliferation in cirrhosis. The distinction between regenerating nodules and HCC depends on their size. If nodules less than 1 cm are discovered via the US and cannot be defined, they should be looked up with another US in 3-4 months. US-detected nodules larger than 1 cm require further imaging, such as contrast-enhanced CT or MRI. HCC is diagnosed by a contrast increase in the vascular phase (wash-in), followed by its elimination in the venous phase [23].

A meta-analysis of the clinical effectiveness of CT and MRI (Figure 1.1) for assessing HCC found that MRI had greater per-lesion sensitivities than multidetector CT, making it the recommended imaging modality for patients who have persistent liver disease [24]. If the initial radiologic test is unclear, confirming with a different technique is advised. If the diagnosis is still questionable, serum AFP levels above 400 ng/mL have a significant positive predictive value. Percutaneous biopsy for HCC should only be performed on nodules that are not typical on CT or MRI scans.

Treatment

Resection: In individuals with significant liver functional reserve, possibly curative partial liver removal is the best therapy for HCC. Solitary HCC restricted to the liver is excellent for surgical resection since there is no radiographic proof of hypertension in the portal vein, no hepatic vascular invasion, and the hepatic function is intact. In well-chosen individuals, relapse-free Long-term survival rates average 40% or higher, with five-year survival rates reaching 90%. The preoperative examination should concentrate on the likelihood that the illness will be limited to the liver, as well as whether the anatomic ties between the intrahepatic tumor and the deeper liver function will allow for resection.

Surgeons limit resection to patients with tumors < 5 cm in diameter, however, there is no universal standard for determining tumor size for resection. Individuals with a single HCC without vascular spread had a similar survival

rate, regardless of tumor size, while individuals with smaller tumors seemed to have a better result.

Hepatic reserve evaluation is critical in choosing patients for amputation. Perioperative recovery fatality is double as high in bleeding individuals as in non-cirrhotic individuals unless effective patient selection is done. Individuals with Child-Pugh class (A) liver disease, who have normal bilirubin levels and good liver function, can safely undergo surgical resection.

Before doing a significant surgical liver excision in certain individuals, hepatic volumetry and the portal vein integrity should also be evaluated.

The precise location and grading of tumors are made possible by the use of intraoperative US. Some gastrointestinal surgeons prefer to do segment-wise hepatectomies during surgical resection, giving respect to anatomy wherever possible. This is dependent on the expectation that the initial section from which the tumor originated would have microscopic intrahepatic metastasis. Interestingly, latent metachronous multicentric neoplasia or intrahepatic metastases induce recurrent HCC to occur in 80% of cases within five years, even after effective surgical resection [25].

Liver Transplantation

Almost every patient who qualifies for a liver transplant is incurable due to the severity of underlying liver disease rather than the size of the tumor. For individuals with end-stage liver disease and early-stage HCC, liver transplantation may be a suitable course of therapy. When a patient has cirrhosis or other chronic liver disease and cannot tolerate liver resection, OLT is a good option [25]. The patient must meet the Milan criteria, which include having a single HCC focal mass with a diameter of no more than 5 cm or up to three different focal lesions, none larger than 3 cm, no evidence of gross assault of vascular structure, no distant metastases, and no regional nodes.

Someone discovered that transplant results were equal for patients who satisfied the University of California, San Francisco criteria (one tumor < 6.5 cm or ≤ three tumors with the biggest tumor diameter ≤ 4.5 cm and total tumor diameter ≤ 8 cm) but did not meet the Milan criteria. Long wait times for donor organs are a significant drawback of organ transplantation (OLT), in addition to the requirement for lifelong immunosuppression and its associated hazards. Since there is still a waiting list of potential recipients, the need for livers is increasing. A global problem is the scarcity of available organ donors. Up to 25% of individuals on 12-month waiting lists are anticipated to be turned down for liver transplants as a result of tumor development [24,26].

Radiofrequency Ablation

RFA has been the most often studied approach when it comes to loco-regional intervention ablation treatment for HCC. Different kinds of electrodes are available for clinical RF ablation, such as multi-tined inflatable electrodes with or without oxygenation and internally cooled electrodes [27]. The elevation of temperatures and ensuing damage are influenced by both the extent of warmth that is attained inside the cell walls and the length of the heating process. Tumor tissue suffers permanent cellular damage after four to six minutes at a temperature rise of 50 to 55 degrees Celsius. Moreover, at temperatures above 100–110 degrees Celsius, tissue vaporizes and carbonizes.

Destroying every live tumor tissue and most likely leaving a good tumor-free margin is a crucial component in achieving effective radiofrequency ablation. Ideally, the tumor should have an ablative border surrounding it that is 360 degrees and 0.5–1 cm thick. This threshold would confirm that tiny incursions surrounding a tumor's margin had been removed. A single tumor with a diameter of less than 4 cm yields the greatest results, while there is no specific tumor size beyond which RFA should not be used. As was already mentioned, RFA has also been applied as a "bridging" treatment. The effectiveness of RFA vs percutaneous ethanol infusion (PEI) in the treatment of early-stage HCC has been examined in five randomized controlled trials (RCTs) [28].

Microwave Ablation

The phrase "microwave ablation" in medicine refers to any electromagnetic technique that uses multiple devices with varying frequencies (which is equivalent to or over 900 kHz) and damages tumors. The various molecules rotate as a result of the microwaves passing through the mitochondria or other substances that contain water. These molecules rotate quickly, which results in a steady and uniform distribution of heat that lasts until the radiation stops entirely. According to the type of cellular needle used and the level of power generated, a circular or column-shaped necrosis region is formed around the needle by microwave irradiation [29].

It must be acknowledged that microwave ablation technology has advanced significantly. The tiny coagulation area created by just one probe insertion appears to have been a constraint solved by newer devices. Compared to radiofrequency ablation, microwave ablation has a significant benefit in that the location of the tumor has no bearing on the treatment's result [28].

Trans Arterial Chemoembolization (TACE)

TACE has been widely utilized to treat HCC which is incurable. The hepatic artery provides the majority of the blood flow

to HCC lesions, whereas the portal system gives blood to the surrounding liver tissue. This is the basis of the TACE concept. For several or large focal HCC lesions, as well as in situations where there is a reduced hepatic reserve, TACE is preferred. The catheter tip is inserted into the HCC lesion's feeding artery at the closest and most accessible location. An emulsion of lipiodol and anti-cancer drugs was injected carefully, followed by the injection of gelatin sponge particles, all under the observation of fluoroscopic monitoring.

The size of the tumor and the extent of the lesions are taken into consideration while calculating the dose of lipiodol emulsion and chemotherapeutic drug used in TACE. In a more modern approach to chemoembolization, drug-eluting polyvinyl alcohol microspheres, or "beads," are used; this approach appears to have comparable effectiveness but less toxicity [25]. When drug-eluting beads are used, the hepatic artery's feeding branch is simultaneously or successively blocked until the blood supply to the tumor tissue stops, which may increase the anti-cancer medication's effectiveness beyond that of chemotherapy alone.

When it comes to downsizing HCC tumors that don't meet transplant requirements, TACE is the first line of defense. Dynamic CT or MRI scans have been performed every three to four months for follow-up, and TACE has been evaluated in cases of intrahepatic metastasis, second main HCC, and/or local recurrence. TACE's limitations include the tumor's extracapsular development, invasion of the liver capsule, and thrombosis-related vascular invasion. When treating advanced HCC tumors that are not responsive to resection or ablation, the TACE should be taken into consideration because complete elimination and destruction of whole tumors are uncommon outcomes.

TACE is the first-line treatment for downstaging HCC tumors that do not meet the transplantation requirements. During follow-up, dynamic CT or MRI was performed every 3 to 4 months, and TACE was considered if local recurrence, second primary HCCs, or intrahepatic metastases were discovered. TACE has limitations such as invasion of the liver capsule, extracapsular tumor development, and thrombosis-induced vascular invasion. Total ablation and necrosis of entire lesions are uncommon; hence TACE should be explored for advanced HCC tumors that cannot be cured by excision or ablation [30].

Cryoablation

Cryoablation is the use of alternating freeze-thaw cycles using a cryoprobe placed directly into the tumor; this method is utilized intraoperatively more commonly in HCC patients with unresectable tumors. RFA has replaced the use of interventional cryoablation [30].

Molecularly Targeted Therapy (sorafenib)

Sorafenib, an oral multi-tyrosine kinase inhibitor, is now thought to be the first medication to enhance survival in patients with advanced HCC. The 2007 multicenter European randomized SHARP trial established monotherapy with sorafenib as the recommended systemic treatment for advanced HCC tumors [30].

A 31% lower relative risk of mortality was seen in a large, double-blind, saline-controlled phase 3 research, with the estimated average overall survival in months rising from 7.9 in the group given a placebo to 10.7 with the sorafenib side (HR = 0.69; 95%CI: 0.55-0.87; P = 0.00058).

A startling finding from a randomized phase II trial contrasting the outcomes of sorafenib plus doxorubicin vs doxorubicin alone indicated an advantage for paired therapy; however, whether the combination is superior to sorafenib alone will require a randomized trial in which sorafenib is used as the control arm.

Cytotoxic Chemotherapy

Chemotherapy is not used regularly for the management of advanced HCC for a variety of reasons, including the tumors' greater resistance to chemotherapy. This is due in part to the high rate of drug resistance gene expression, which includes alterations in p53, glutathione-S-transferase, P-glycoprotein, and heat shock proteins; (2) systemic chemotherapy is typically not recognized and tolerated by patients due to significant underlying poor hepatic reserve. The degree of damage of hepatic reserve is most often used to estimate patients' overall survival, rather than tumor aggressiveness or the impact of systemic treatment; (3) clinical trials of systemic therapy for individuals with advanced stage HCC have been conducted in various populations.

Despite these issues, emerging data suggest a modest antitumor efficacy for several cytotoxic agents or combined drug regimens; a chemotherapy trial may be warranted in many individuals, particularly if they have normal underlying liver. Reactivation of viral hepatitis is possible in HCC patients undergoing intensive systemic chemotherapy; consequently, antiviral medicines must be continued.

Using a combination therapy of intra-arterial infusion of 5-Fluorouracil (5-FU) and subcutaneous interferon in 116 HCC patients with portal vein invasion has shown promising results [30,31].

Conclusion

HCC is an invasive malignancy that develops in the presence of ongoing liver disease and fibrosis and often appears in

advanced stages. Concomitant liver impairment during advanced tumor stages complicates curative therapy and other malignancies can be avoided with effective methods such as the HBV vaccine, blood product screening, secure injection procedures, treatment, and lessons for drinkers, as well as those who use intravenous drugs and antivirals. HCC surveillance is based on US testing every 6 months since AFP lacks the sensitivity and specificity required for reliable surveillance and diagnosis. Several clinical trials are underway in pursuit of a more effective technique. MicroRNAs are one of these technologies, and they show promise as both a diagnostic and predictive tool for HCC. HCC treatment is determined by an assessment of the state of the tumor using BCLC or other grading methods, as well as the patient's hepatic function and performance status. Improved surgical and nonsurgical methods have significantly increased overall survival rates. Although OLT is the only curable surgical surgery for HCC, it is not accessible for many patients due to organ shortages. Sorafenib is a novel neo-antigenic targeted agent with promising effects. Further research is needed to quantify the survival and regression of tumors using several biomarkers, both alone and in combination with other modalities.

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