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HEPATOCARCINOMA: FROM RISK FACTORS TO IMMUNOTHERAPY. THE ROLE OF AWARENESS AND EARLY DETECTION: A NARRATIVE REVIEW

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ABSTRACT

BACKGROUND:

Hepatocellular carcinoma (HCC) is one of the most common and deadly liver malignancies worldwide. Its rising incidence is linked not only to viral hepatitis and cirrhosis, but increasingly to metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease. Most cases are diagnosed at advanced stages, when curative treatment options are limited. In recent years, immunotherapy has emerged as a promising systemic strategy.

OBJECTIVE:

This narrative review aims to summarize current knowledge on the pathogenesis, risk factors, diagnostic approaches, and especially immunotherapeutic strategies for HCC, with a focus on immune checkpoint inhibitors and their clinical relevance.

METHODS:

A non-systematic narrative review was conducted using PubMed and Google Scholar. The search included English-language publications from January 2015 to March 2024. Search terms included combinations of "hepatocellular carcinoma," "HCC," "immune checkpoint inhibitors," "PD-1," "PD-L1," "CTLA-4," and "tyrosine kinase inhibitors." Preference was given to peer-reviewed research articles, clinical guidelines, and high-quality reviews.

RESULTS:

Immunotherapy, particularly the use of immune checkpoint inhibitors such as nivolumab, pembrolizumab, and the combination of atezolizumab with bevacizumab, has shown clinical benefits in patients with advanced HCC. These agents enhance antitumor immune responses by targeting inhibitory pathways such as PD-1/PD-L1 and CTLA-4. Despite these advances, treatment response rates remain limited, and most patients experience disease progression. The immunosuppressive tumor microenvironment and lack of predictive biomarkers present major therapeutic challenges.

CONCLUSION:

While immunotherapy has expanded the treatment landscape for HCC, it is not curative for the majority of patients. Ongoing research is needed to refine combination strategies, identify reliable biomarkers of response,

and improve early detection, particularly in populations with metabolic risk factors.

Keywords: hepatocellular carcinoma; immunotherapy; immune checkpoint inhibitors; PD-1; CTLA-4; TKI.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related mortality worldwide, following lung and colorectal cancers [1,2,3]. According to global cancer statistics, approximately 906,000 new cases and 830,000 deaths were reported in 2020 [1]. Men are affected significantly more often than women, with an estimated male-to-female ratio of 3 to 1 [4]. Projections by the World Health Organization indicate that liver cancer mortality may exceed one million deaths annually by 2030 [5].

The rising incidence of HCC is closely associated with the increasing prevalence of metabolic disorders, such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease [6]. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) also remain major risk factors, particularly in regions with limited access to early diagnosis and antiviral therapy [12,13]. HCC accounts for 75 to 85 percent of all primary liver cancers [3], while other malignancies such as intrahepatic cholangiocarcinoma, hepatoblastoma, and hepatic sarcomas occur less frequently [7].

In Poland annual incidence of primary liver cancer, predominantly hepatocellular carcinoma, is estimated at 1 600–2 500 new cases, with approximately the same number of deaths reported each year [31]. A regional study in northeastern Poland confirmed this figure [31]. In 2016 approximately 895 men and 588 women were diagnosed with HCC in Poland, while total HCCrelated deaths reached about 2 024 cases (1 145 men and 879 women) [32]. These data reflect a rising trend in the burden of HCC and underscore the need for timely diagnosis and improved access to effective therapies.

Early-stage HCC may be treated with surgical resection, liver transplantation, or local ablative techniques. However, the majority of cases are diagnosed at an advanced stage, when curative options are no longer viable. Available systemic therapies, such as sorafenib and lenvatinib, provide only limited survival benefits, typically extending life expectancy by two to three months [1,4,6]. This highlights the critical need for novel treatment approaches that are more effective and better tolerated.

In recent years, considerable attention has been given to the immunological aspects of HCC. The liver is an immunologically unique organ with inherent tolerance mechanisms that protect against excessive responses to dietary and microbial antigens. However, these same mechanisms can suppress antitumor immunity and facilitate immune evasion by malignant cells [11,24]. The tumor microenvironment of HCC is characterized by a complex network of immunosuppressive cells, cytokines, and checkpoint molecules that inhibit effective immune responses [9,25].

Advances in immunotherapy have led to the development of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4. These agents have shown promising efficacy in patients with advanced HCC and are currently approved in various clinical settings [1,22]. Nevertheless, treatment response remains variable, and immune-related adverse events present important clinical challenges [4,22,30].

This review provides an up-to-date synthesis of current knowledge on hepatocellular carcinoma, with emphasis on risk factors, diagnostic methods, and therapeutic strategies. Special focus is placed on the role of the immune system in HCC pathogenesis and on recent progress in immunotherapy, including current evidence, mechanisms of action, and limitations of immune checkpoint blockade.

METHODS

A non-systematic narrative review was conducted using electronic databases including PubMed and Google Scholar. The search included articles published in English between January 2015 and March 2024.

Search terms included combinations of "hepatocellular carcinoma," "HCC," "immunotherapy," "immune checkpoint inhibitors," "PD-1," "PD-L1," "CTLA-4," and "tyrosine kinase inhibitors." Preference was given to peer-reviewed original research articles, systematic reviews, meta-analyses, and official clinical guidelines. Editorials, case reports, and non-English articles were excluded. Reference lists of included articles were also screened to identify additional relevant publications.

FINDINGS AND DISCUSSION

EPIDEMIOLOGY

More than 800,000 people worldwide die from hepatocellular carcinoma (HCC) each year, making it the third most

common cause of cancer death [4]. There are significant regional differences in HCC incidence and mortality, due in part to differential exposure to risk factors - both environmental and infectious - as well as unequal access to health care, including early-stage diagnosis and treatment [12]. As many as 80% of HCC cases are reported in sub-Saharan Africa and East Asia, where the predominant risk factors are chronic hepatitis B virus infection and contact with aflatoxin B1. In HBV (Hepatitis B Virus) infected individuals, the risk of developing HCC increases with the severity of the viral load, the duration of infection, and the degree of liver damage [13]. In the case of hepatocellular carcinoma caused by HBV infection, the most commonly diagnosed patients were in the age range of 32.5-37.5 years [12]. In contrast, in Western European, North American, and Japanese countries, the main cause of the development of this cancer is hepatitis C virus (HCV - Hepatitis C Virus) infection [14]. In recent years, an increase in the incidence of HCC has been observed in the United States and Central Europe, most likely due to the growing problem of obesity and HCV transmission, especially among intravenous drug users. Meanwhile, regions historically characterized by high liver cancer incidence rates have seen a decline, likely related to the widespread introduction of HBV vaccination [15]. Non-alcoholic steatohepatitis (NASH) is gaining increasing importance as a risk factor for HCC in developed countries, and is rapidly becoming one of the leading causes of cancer. Between 2010 and 2019, NASH was responsible for the fastest increase in HCC-related deaths worldwide [2].

RISK FACTORS

The risk of developing hepatocellular carcinoma (HCC) is due to several factors that include biological, environmental, and demographic aspects. Among the most relevant are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, aflatoxin B1 (AFB1) exposure, excessive alcohol consumption, metabolic steatohepatitis (MASH), and factors such as gender, age, and ethnicity [6,16]. In developing countries, HBV is responsible for about 60% of all HCC cases [15]. Globally, as many as 257 million people are living with chronic HBV infection. It is estimated that between 2015 and 2030, about 20 million deaths will be associated with acute hepatitis, chronic forms of the disease, cirrhosis, and liver cancer caused by HBV, of which about 5 million cases will be directly related to HCC [12]. In more than 85% of HBV-induced cancer cases, patients have co-occurring cirrhosis [6]. In endemic regions, HBV transmission is mainly through contact with infected blood, often through vertical transmission from mother to child in the womb or during childbirth, as well as through horizontal transmission, such as between family members. Despite the existence of effective prophylaxis in the form of neonatal vaccination, the vaccination rate in some heavily populated African countries with a high incidence of HCC is only 40-70%. However, there is evidence that the use of antiviral therapy in women in the third trimester of pregnancy with high levels of the virus can significantly reduce the risk of neonatal infection [12]. Although treatment of chronic HBV infection still does not lead to a complete cure, an effective and safe vaccine provides almost 100 percent protection against infection, and available antiviral therapies can significantly slow the progression of liver disease [7]. An equally important risk factor for HCC, especially in developed countries, such as Japan, the US, and European countries, is HCV infection. Unlike HBV, HCV does not integrate into the host's DNA. Its presence in liver cells induces chronic inflammation, which over time leads to cell death, fibrosis, followed by cirrhosis and cancer [6]. Approximately 30% of HCV-infected patients experience spontaneous elimination of the virus within six months, while the remaining 70% develop a chronic form of infection [7]. In some regions of the world, there are also cases of HBV and HCV co-infection, which further increase the risk of developing HCC [7]. A breakthrough in the treatment of HCV came with the introduction of direct-acting antiviral (DAA) drugs, which allow for the successful cure of more than 95% of those infected [7,13]. Currently, there is no vaccine against HCV, but prophylaxis through safe medical practices, such as the use of disposable equipment, blood testing before transfusion, and proper sterilization of surgical and dental instruments, is key to reducing HBV and HCV transmission [12]. Although HBV remains the most important factor responsible for the incidence of HCC worldwide, non-alcoholic fatty liver disease (NAFLD) has become the fastest-growing cause of HCC over the past two decades, especially in the US, Europe, and Southeast Asia [5]. Non-alcoholic fatty liver disease (NAFLD) currently dominates as the most common liver disease in developed countries and is a key contributor to hepatocellular carcinoma (HCC). In the United States, NAFLD accounts for 10-20% of all HCC cases, and the risk of developing HCC in people with NAFLD increases more than 2.5-fold [12]. At the same time, there is a worldwide increase in the prevalence of modifiable risk factors, such as excessive alcohol consumption and metabolic syndrome [14]. Diabetes is an independent risk factor for HCC. Studies have shown that men with an elevated body mass index (BMI) are five times more likely to die from liver cancer compared to those with a normal BMI [13]. Diabetes can even double or triple the likelihood of HCC. Insulin resistance leading to increased production of reactive oxygen species and chronic inflammation is thought to play an important role in the development of this cancer [12]. Another significant risk factor is alcohol. Its excessive consumption not only increases the chances of developing liver cancer, but also other cancers, including throat, colon, breast, and stomach. The risk increases proportionally to the amount of ethanol consumed - consuming 50 grams a day raises the risk by 46%, and 100 grams a day by as much as 66% compared to abstainers [7]. Studies have shown that consumption of more than three servings of alcohol per day is associated with a 16% increase in the risk of HCC [14]. An early consequence of excessive alcohol consumption is alcoholic fatty liver (AFL), which is usually asymptomatic. More than 90% of alcohol abusers develop AFL, but only about 30% progress to severe alcoholic liver disease (ALD). Chronic

alcoholic inflammation promotes liver fibrosis through an imbalance between the formation and breakdown of extracellular matrix (ECM) components. In the initial stages, these changes are reversible after cessation of drinking, and new anti-fibrotic therapies have shown promising results. Nevertheless, long-term fibrosis leads to cirrhosis and increases the risk of HCC [7]. Smoking also contributes to the increased risk, while coffee consumption may reduce the risk. Co-infection with HIV and HBV or HCV is associated with faster progression of liver disease and increased incidence of HCC, especially when cirrhosis develops [13]. Metabolic syndrome is another important factor - one study indicated that the presence of this syndrome increases the risk of HCC by as much as 81%. However, it is possible to reduce this risk by treating concomitant disorders such as insulin resistance, overweight, hypertension, and dyslipidemia [14]. Lifestyle changes - particularly alcohol restriction and control of metabolic syndrome factors - play a key role in the prevention of HCC [13]. Aflatoxins, produced by fungi such as Aspergillus flavus and A. parasiticus, are another threat to liver health. These toxic compounds, made up of a furan ring linked to coumarin, are formed as products of secondary fungal metabolism and can contaminate food, especially cereals and nuts, during harvest, transport, or storage. Following their ingestion, various adverse effects can occur, including liver damage, immune system impairment, and teratogenic effects. Of the more than 20 known aflatoxins, the most dangerous is aflatoxin B1 (AFB1), which has potent genotoxic and carcinogenic effects [6,7]. Acute aflatoxin poisoning leads to liver failure manifested by, among other things, jaundice, abdominal pain, and nausea, and in extreme cases can end in death. Long-term exposure to AFB1 has a proven link to the incidence of HCC, especially in Southeast Asian and sub-Saharan African countries, where climatic conditions favor mold growth [7]. Other chronic liver diseases, such as biliary tract diseases or certain genetic and metabolic disorders, can also lead to cirrhosis and ultimately to the development of HCC. However, globally, they account for only 5-10% of cases of this cancer [12]. In terms of HCC prevention, treatment of viral infections with nucleoside and nucleotide analogs in the case of HBV, and interferon in the case of HCV, has had significant effects in reducing the incidence. Additionally, it has been shown that interventions such as weight reduction and the use of medications like statins and metformin can effectively reduce the risk of HCC in high-risk patients [6].

The development of hepatocellular carcinoma is driven by a range of well-established risk factors, both infectious and metabolic. These include chronic hepatitis B and C infection, liver cirrhosis of various etiologies, excessive alcohol consumption, type 2 diabetes, and non-alcoholic fatty liver disease. Table 1 provides an overview of the major risk factors associated with HCC, highlighting their pathophysiological mechanisms and relative prevalence.

Table 1. Major Risk Factors for Hepatocellular Carcinoma

Risk Factor	Mechanism	Epidemiological Notes
Chronic Hepatitis B Virus (HBV) Infection	Integration of viral DNA into host genome, chronic inflammation	Endemic in Asia and sub-Saharan Africa
Chronic Hepatitis C Virus (HCV) Infection	Chronic inflammation and fibrosis leading to cirrhosis	Common in Europe, Japan, and the USA
Cirrhosis (any cause)	Liver regeneration and DNA damage in fibrotic tissue	Present in >80% of HCC cases
Non-Alcoholic Fatty Liver Disease (NAFLD)	Chronic hepatic steatosis, inflammation, and fibrosis	Rapidly increasing in Western countries
Alcohol-related Liver Disease	Hepatocyte injury, inflammation, and cirrhosis	High prevalence in Central and Eastern Europe

DIAGNOSIS

The diagnosis of liver cancer requires an integrated diagnostic approach that includes clinical evaluation as well as imaging and laboratory tests [6]. Primary visualization methods include ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI), while liver biopsy is sometimes performed to definitively confirm the diagnosis [6]. Laboratory tests, including liver tests and alpha-fetoprotein (AFP) determination, are also commonly used in the diagnosis and monitoring of HCC [9]. Ultrasound often serves as a first-line diagnostic tool because of its non-invasiveness, relatively low cost, and lack of risk from ionizing radiation. The effectiveness of this method in detecting HCC is estimated at a sensitivity of 51% to 87% and a specificity of 80% to 100%. Nevertheless, ultrasonography has its limitations, especially in detecting lesions less than 1 cm in diameter and in distinguishing between benign and malignant foci. When diagnostic difficulties arise,

more advanced techniques such as CT and MRI prove helpful. Computed tomography, based on X-rays, provides detailed images of the organ and its surroundings. In the diagnosis of HCC, it has a sensitivity of 63-76% and a specificity of 87-98%. MRI, on the other hand, using magnetic fields and radio waves, offers even greater accuracy, with a sensitivity of 77-90% and a specificity of 84% to 97% [6]. Determination of the level of alpha-fetoprotein (AFP), the most commonly used tumor marker in HCC, is also an important part of diagnosis. This test is useful both in assessing prognosis and monitoring response to treatment [9]. Early detection of HCC, especially in high-risk patients, using non-invasive methods such as ultrasound and AFP determination, can significantly improve survival rates and bring tangible economic benefits, especially in countries with a high incidence of this type of cancer [6].

CLASSIFICATION

A variety of classification systems, such as Barcelona Clinic Liver Cancer (BCLC), Okuda, Cancer of the Liver Italian Program (CLIP), Italian Liver Cancer (ITALICA), and the TNM system developed by the American Joint Committee on Cancer (AJCC), are used to assess the stage of hepatocellular carcinoma (HCC) [6]. The diversity of these methods is due to the high clinical heterogeneity of HCC, regional medical preferences, and different eligibility criteria for surgery or transplantation [15]. The BCLC system divides HCC into five stages labeled 0, A, B, C and D. It takes into account factors such as the size and number of tumors, the presence of vascular infiltration or metastasis, liver function as assessed by the Child-Pugh classification, and the patient's overall performance status [3]. Patients in early stages (0 and A) can be treated radically by resection, transplantation, or ablative therapy. For multifocal disease (stage B), transcatheter chemoembolization (TACE) is recommended, while stage C, characterized by extrahepatic spread or vascular infiltration, is treated with systemic therapy, most commonly sorafenib [15]. In patients with intermediate-stage HCC (BCLC B), TACE treatment achieves a median survival of about 20 months, while for more advanced disease (BCLC C), sorafenib provides a median survival of 10.5 months. There is still a clear need to develop more effective therapies for these patients [17]. Okuda's classification system takes into account both tumor features and the degree of liver failure, based on assessment of the presence of ascites, albumin, and bilirubin levels in the blood, among other factors. Survival rates for untreated patients classified into stages I, II, and III, respectively, average 8.3, 2.0, and 0.7 months [15]. Its limitation is that it does not take into account pathological parameters such as vascular infiltration or lymph node metastasis, making its clinical utility limited, especially in patients eligible for therapy. Another system, CLIP, takes into account the stage of cirrhosis (Child-Pugh), tumor characteristics, the presence of portal vein thrombosis, and serum AFP levels. This scale awards 0 to 6 points and has shown utility in assessing the prognosis of patients with advanced HCC [15]. The TNM system, on the other hand, as updated in 2010 by the AJCC, focuses mainly on tumor characteristics - tumor size (T), lymph node involvement (N), and the presence of distant metastases (M) [7]. Within the T classification, there are four categories (T1-T4), while N is divided into N0 (no node metastasis) and N1 (presence of metastasis). M indicates the presence or absence of distant metastases - M1 or M0, respectively. Five-year survival rates for TNM stages I, II, and III are 55%, 37%, and 16%, respectively [15]. This system, while widely used - especially in the US - has the limitation of not taking into account the patient's liver function [7]. Although a single, universal staging system accepted worldwide has yet to be developed, each of the aforementioned systems makes an important contribution to therapeutic decision-making, disease course prognosis, and stratification of patients with HCC [6].

TREATMENT

Treatment of hepatocellular carcinoma (HCC) is a complex process that requires consideration of many factors, such as the size of the tumor, the patient's comorbidities, and the degree of liver damage. Most treatments for HCC can exacerbate liver problems, requiring caution in the choice of therapy. The availability of treatment options varies according to medical centers and the level of resources and expertise in a given country. Consequently, the treatment of HCC should be based on the collaboration of multidisciplinary teams to achieve the best possible results [12]. Therapies for liver cancer depend on the stage of the disease. Early stages most often require surgical intervention, which provides a 5-year survival in about 70% of patients. When surgery or liver transplantation are not possible, local therapies such as ablation (radiofrequency, thermal, and non-thermal) or chemoembolization are used, which show variability in survival rates over a 3-5 year period [18]. Unfortunately, at the time of diagnosis, only a small proportion of patients are suitable for radical treatment. When surgery is not possible, the tumor can grow, leading to intra- and extrahepatic metastases (mainly to the lungs and bones). In such cases, patients usually die after about 10 months due to tumor cachexia, bleeding from esophageal or gastric varices, liver failure, and, less commonly, peritoneal hematoma secondary to tumor rupture [8]. In advanced, inoperable HCC, available systemic therapies such as sorafenib, regorafenib, and lenvatinib offer limited survival benefit [19]. Immunotherapy, particularly therapies focusing on immune checkpoint inhibitors (ICIs), has evolved significantly in the last decade. By blocking checkpoints such as PD-1, PD-L1, or CTLA-4, these therapies activate cytotoxic CD8+ T cells, effectively preventing tumor cells from escaping the immune system [18].

RESECTION

Surgical resection is the preferred treatment for patients with hepatocellular carcinoma (HCC) whose disease is resectable and when there is no clinically significant portal hypertension [12]. If the location and size of the tumor are suitable, segmental or subsegmental resections are preferred [8]. Eligibility for the procedure requires that the tumor is located in surgically removable areas and the patient has adequate liver reserve, as assessed by clinical and biochemical methods. Resection is recommended for patients with a well-functioning liver, usually in Child-Pugh class A [15]. Before surgery, it is necessary to perform liver volumetry using CT scans and assess the degree of portal hypertension, preferably by measuring the hepatic venous pressure gradient, which should not exceed 10 mmHg. There are also indirect methods, such as endoscopy to detect esophageal varices and evaluation of platelet counts, a drop below 100,000/mm3 may indicate the presence of portal hypertension. Detection of portal hypertension, regardless of the method of measurement, is a relative contraindication to hepatectomy. The functional reserve of the liver before surgery and the ability to regenerate after surgery are crucial, both of which affect the risk of liver failure. Inadequate function of the remaining liver, defined as "small relative to size," manifests symptoms of failure, including hyperbilirubinemia, encephalopathy, and coagulopathy. After hepatectomy, the minimum volume of the remaining liver should be between 20% and 40% of the total volume [8]. Long-term surgical outcomes depend on factors such as the degree of vascular infiltration, the number of nodules, their size, and the status of the surgical margin [15]. Although tumor size is not an immediate limitation, the risk of vascular infiltration and spread of disease increases with increasing tumor diameter [13]. The optimal surgical margin is 2 cm [8]. Recurrence remains a major challenge after resection, and occurs in more than 50% of patients [2]. Treatment of recurrence includes repeat hepatectomy, TAE/TACE, radiofrequency ablation, or salvage liver transplantation [15]. Five-year survival after surgery can be 70-80% [6].

LIVER TRANSPLANTATION

Liver transplantation is the definitive treatment option for hepatocellular carcinoma (HCC), as it removes not only the tumor, but also the damaged liver, whose function is limited and which tends to develop new tumors within the margin tissue, prone to carcinogenesis [12]. The Milan criteria, developed by Mazzaferro, specify that liver transplantation is indicated for a single tumor ≤5 cm in diameter or up to three tumors, the largest of which is ≤3 Cm, provided there is no evidence of infiltration of large vessels or metastasis outside the liver [15]. With liver transplantation, the 10-year survival rate is 50-60%, and the risk of recurrence is 10-20% [6]. The biggest limitation of liver transplantation is the shortage of donors, which leads to the need to wait for transplantation. During this time, the tumor can grow, making the procedure more difficult [13]. Treatment of HCC before transplantation has three goals: controlling tumor growth and vascular infiltration while waiting, which reduces the risk of removing a patient from the waiting list; using neoadjuvant therapy to improve post-transplant outcomes by reducing the risk of post-operative recurrence; and reducing the burden of HCC so that the patient is eligible for transplantation. Patients on the waiting list must undergo follow-up examinations every three months, such as CT scans, MRIs, and determination of serum AFP levels, to ensure that they still meet transplant criteria [10]. Various invasive radiologic procedures, such as transarterial TACE chemoembolization, TAE, radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI), can be used to control tumor disease [8].

TUMOR ABLATION

Tumor ablation is an established treatment option for patients with early-stage hepatocellular carcinoma. The technique involves inducing tumor necrosis by changing the temperature (using radiofrequency, microwave, laser, or cryoablation) or injecting chemicals, most commonly ethanol [13]. The ablation procedure is usually performed percutaneously by inserting needles under ultrasound or CT guidance [20]. Microwave ablation is less affected by heat absorbed by large blood vessels adjacent to the tumors, making it more effective for larger tumors (3-4 cm) and requiring less time than radiofrequency ablation [12]. RFA (radiofrequency ablation) works through a needle placed close to the tumor lesion, which is connected to a radiofrequency wave generator. These waves are converted into heat, which heats the tumor, leading to thrombotic necrosis. RFA is used for tumors up to 5 cm and can be part of pre-transplant treatment or palliative therapy. A contraindication to this method is the presence of large vessels or biliary branches near the tumor [8]. Percutaneous ethanol ablation (PEI) involves the injection of ethanol (96% alcohol) through a needle inserted into the tumor under image guidance, which causes protein denaturation and tumor cell death [8]. Locoregional ablation can also act as a bridging therapy before liver transplantation [12].

LOCAL-REGIONAL THERAPY

Transcatheter cancer therapies using imaging are designed to induce tumor necrosis based on the difference in vascularization between hepatocellular carcinoma and healthy liver parenchyma. This difference in vascularization allows selective delivery of drugs, embolic particles, or radioactive substances directly to the tumor [13]. Transarterial chemoembolization (TACE) is an effective treatment for patients with intermediate-stage HCC. The procedure consists of two main steps: injection of cytotoxic chemotherapeutic drugs into the artery supplying the tumor, and delivery of embolization particles, which leads to tumor necrosis due to ischemia. The most commonly

used drugs in conventional TACE include doxorubicin, epirubicin, and cisplatin [12]. Advances in the development of polyvinylidene beads, which allow precise embolization with concomitant slow release of chemotherapy, have made it possible to standardize the procedure while maintaining efficacy and minimizing side effects [13]. By precisely targeting the blood vessels of the tumor, TACE limits the exposure of the rest of the body to chemotherapy [6]. The most common complication of TAE/TACE is post-embolization syndrome, which can occur in up to 80% of patients, manifesting as fever, abdominal pain, and an increase in alanine aminotransferase levels [15]. TACE is a frequently used local-regional treatment among patients qualified for liver transplantation to prevent tumor progression. Survival outcomes after TACE depend on the size of the tumor and the degree of liver dysfunction, showing great variability. Transarterial radioembolization (TARE) is another local treatment technique that is particularly useful in the treatment of inoperable HCC. TARE is a form of intra-arterial brachytherapy in which radioactive microspheres containing the isotope yttrium-90 are delivered to the arteries supplying the HCC tumor, allowing higher radiation doses to be achieved than with external radiation therapy. Unlike TACE, TARE causes minimal vascular occlusion, making it a treatment option for patients with portal vein thrombosis or tumor infiltration [12].

SYSTEMIC THERAPY

Systemic therapy is the mainstay of treatment for advanced hepatocellular carcinoma (HCC) [21]. Since the beginning of the 21st century, molecularly targeted drugs have become crucial in the treatment of various types of cancer [22]. Receptor tyrosine kinases (RTKs) play an important role in regulating basic cellular processes such as cell differentiation, proliferation, and survival. Studies have shown that several RTKs are involved in the development of HCC. These molecular pathways can be blocked by targeted therapy, using monoclonal antibodies or tyrosine kinase inhibitors (TKIs) [3]. Molecularly targeted drugs such as sorafenib, lenvatinib, donafenib, regorafenib, cabozantinib, ramucirumab, and apatinib are the mainstay of systemic therapies for advanced HCC. Sorafenib, which is the first approved multi-target RTK inhibitor, has been used as first-line treatment for HCC since 2007 [21].

SORAFENIB

Sorafenib is a small-molecule multikinase inhibitor that affects VEGFR1, VEGFR2, and VEGFR3 receptors, PDGFRβ, and Raf family kinases (mainly C-Raf) [12,22]. It was approved by the FDA in 2007 for the treatment of inoperable HCC [3]. The SHARP trial, a multicenter, randomized, controlled trial involving 602 patients, showed that median overall survival (OS) was 10.7 months in the sorafenib-treated group, compared to 7.9 months in the placebo group (risk ratio 0.69, 95% CI 0.55-0.87; p<0.001). The frequency of serious adverse reactions was 9.4-14.6% in the sorafenib group and 5.0-25% in the placebo group. The most common side effects included diarrhea, weight loss, and skin lesions of the hands and feet [23].

LENVATINIB

Lenvatinib is a multi-kinase inhibitor that acts on VEGFR, FGFR, PDGFRα, RET, and KIT [14]. It was approved by the FDA in 2018 for the treatment of inoperable hepatocellular carcinoma as a first-line therapy. A phase 3 clinical trial showed that lenvatinib was no worse than sorafenib in the treatment of HCC, with a median OS of 13.6 months in the lenvatinib group, compared to 12.3 months in the sorafenib group (HR = 0.92; 95% CI 0.79-1.06) [3]. The main side effects of lenvatinib were hypertension, proteinuria, and diarrhea [23].

REGORAFENIB

Regorafenib is an oral multidrug that inhibits PDGFR-β, VEGFR1-3, Tie-2, c-Kit, FGFR-1, Ret, RAF-1, BRAF, and p38. It was approved by the FDA in 2017 to treat patients with HCC who had previously received sorafenib. The most common serious side effects included hypertension (15%), hand-foot skin reaction (13%), increased bilirubin and AST levels (10% each), and fatigue (9%) [3].

CABOZANTINIB

Cabozantinib is an oral tyrosine kinase inhibitor that acts on VEGFR1-3, RET, MET, and AXL. It was approved by the FDA in 2019 for the treatment of HCC in patients previously treated with sorafenib [3].

TUMOR MICROENVIRONMENT

The immune system plays a key role in controlling cancer progression. Its two components - innate and adaptive - work together to enable effective immune surveillance of cancer development [9]. The liver, a central organ in regulating the immune response, maintains a balance between inducing immune tolerance to avoid damage to the body and activating the immune response to eliminate pathogens [24]. Abnormal interactions between the tumor and the immune system can lead to evasion of the immune response, including through impaired antigen recognition or the formation of an immunosuppressive tumor microenvironment (TME) [9]. The liver is

characterized by an internal microenvironment that promotes immunosuppression, which is a barrier to the effectiveness of immunotherapeutic interventions [19]. The TME includes a variety of cells, cytokines, and other components, including Kupffer cells, hematopoietic stem cells, hepatic stellate cells (HSCs), dendritic cells (DCs), regulatory T cells (Treg), and liver sinusoidal endothelial cells (LSECs) [11,25]. Kupffer cells, which are liver macrophages, play a key role in the innate immune system by creating an immunosuppressive environment and inducing immune tolerance [24]. These cells produce inhibitory molecules, such as IL-10 and prostaglandins, and activate Treg cells [9]. In HCC, Kupffer cells overexpress PD-L1, which blocks CD8+ T-cell activity and prevents elimination of tumor cells [24]. Liver sinusoidal endothelial cells (LSECs) also express high levels of PD-L1, which promotes Treg activation through TGFβ. Hematopoietic stem cells (HSCs) secrete hepatocyte growth factor (HGF), which leads to the accumulation of MDSCs and T cells in the liver and can induce T-cell apoptosis through PD-L1 expression [9]. Another mechanism that promotes natural immune tolerance in the liver is immune checkpoints, which prevent excessive activation of effector lymphocytes. This avoids damage to normal tissue and maintains the body's immune tolerance [11]. Understanding the mechanisms by which immune cells allow tumors to evade the immune response is key to developing effective immunotherapeutic strategies [25]

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoints are inhibitory receptors expressed by immune effector cells that play a role in regulating immune tolerance, preventing excessive responses from the body [1]. They provide a molecular mechanism for the physiological control of the immune response, limiting the risk of excessive immune response [22]. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block interactions between checkpoint proteins and their ligands, preventing T-cell inactivation [9]. In the context of cancer, cancer cells use these inhibitory mechanisms to evade the immune response and promote immunosuppression, which reduces the cytotoxic capacity of T cells [3]. To date, several checkpoint inhibitors targeting proteins such as CTLA-4, PD-1, and its ligand PD-L1 have been approved by the FDA for the treatment of various cancers, including HCC [1].

PD-1/PD-L1

PD-1 is a member of the CD28 family and is present on the surface of many immune cells, especially on activated T cells, natural killer (NK) cells, regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs), monocytes, and dendritic cells (DCs). PD-1 binds to PD-L1 and PD-L2 ligands, which are present on the cell surface in various cancers, including HCC, where they transmit inhibitory signals to T cells, leading to immune escape of cancer cells [1]. In the HCC tumor microenvironment, PD-L1 is mainly expressed in Kupffer cells, but is also found to a lesser extent on other APCs and tumor cells [26]. In 2017, the PD-1 inhibitor, nivolumab, received accelerated registration in the US for second-line treatment of patients with advanced HCC, following treatment with sorafenib [1]. Higher PD-L1 expression in HCC is associated with a poorer prognosis in patients with the disease [26]. Studies have shown that overexpression of PD-L1 correlates with greater tumor aggressiveness and a higher risk of postoperative recurrence in patients with HCC [15]. Clinical data further support that PD-L1 plays a key role in disease progression and is an important target for liver cancer treatment [26,27]. PD-1/PD-L1-related pathways are fundamental to cancer immunotherapy, and their inhibitors have provided breakthroughs in treatment, offering hope to patients with hepatocellular carcinoma [11].

NIVOLUMAB

Nivolumab, an anti-PD-1 antibody, is the first approved immune checkpoint inhibitor (ICI) for the treatment of HCC [22]. It is a human IgG4 monoclonal antibody that blocks interactions between PD-1 and its ligands PD-L1 and PD-L2 [11]. In the CheckMate 040 trial, the median response time to nivolumab in a group of 48 patients in the dose escalation cohort was 17 months, and the two-year survival rate among patients who responded to treatment exceeded 80% [1]. Based on the results of this study, the FDA approved nivolumab as a second-line systemic treatment for patients who had previously been treated with sorafenib [11]. PD-L1 expression above 1% was associated with better survival outcomes in patients receiving nivolumab. In contrast, worse survival outcomes were observed in patients with impaired liver function (Child-Pugh B and C), jaundice, albumin levels ≤3.5 g/l, elevated liver enzymes, increased CRP levels, and higher neutrophil-to-leukocyte ratio. Interestingly, patients with larger pulmonary lesions (more than 30 mm) responded better to nivolumab treatment compared to those with smaller lesions or no pulmonary lesions [3].

PEMBROLIZUMAB

Pembrolizumab, another antibody targeting PD-1, has shown comparable efficacy to nivolumab [22]. It initially gained accelerated approval for second-line treatment of advanced hepatocellular carcinoma, achieving a response rate (ORR) of 17% and a median overall survival (mOS) of 12.9 months [14]. 14% of patients experienced therapy-related adverse events (IrAE), including hypothyroidism, adrenal insufficiency, and thyroiditis [3].

ATEZOLIZUMAB

Atezolizumab is a monoclonal antibody directed against PD-L1. In combination with bevacizumab, atezolizumab reduced the risk of death (OS) by 56% and the risk of disease progression or death (PFS) by 40% compared to sorafenib. In addition, the combination of atezolizumab and bevacizumab is well tolerated, and side effects are easily controlled. In May 2020, the combination was approved by the FDA as the first immunotherapy for the first-line treatment of inoperable hepatocellular carcinoma [11].

DURVALUMAB

Durvalumab, a humanized IgG1 monoclonal antibody directed against PD-L1, has been evaluated as a monotherapy for the treatment of inoperable HCC. According to the 2022 NCCN guidelines, durvalumab is recommended for use in the first-line treatment of advanced liver cancer [11].

CTLA-4

CTLA-4, which is a homolog of CD28, is mainly found in the intracellular compartments of resting naive T cells. Its role is to inhibit T cell responses by delivering inhibitory signals and interfering with the interaction between B7 and CD28. In addition, CTLA-4 is important for the function of regulatory T cells (Treg), which control effector T cell activity and play a key role in maintaining peripheral tolerance. Unlike effector T cells, Treg cells continuously express CTLA-4, which allows them to exert immunosuppressive effects. Ipilimumab and tremelimumab are CTLA-4 inhibitors, with Ipilimumab being the first such drug approved by the FDA in 2011 for the treatment of advanced skin cancer [1].

TREMELIMUMAB

Tremelimumab is an IgG2 monoclonal antibody directed against CTLA-4 [1,17]. In a 2013 clinical trial, tremelimumab demonstrated potent anti-tumor activity, achieving a partial response (PR) rate of 17.6% and a disease control rate of 76.4% [4]. The most common grade 3 or higher adverse effects included increased AST and ALT levels in 45% and 25% of patients, respectively, increased total bilirubin in 10%, neutropenia in 5%, and diarrhea and rash in 5% of participants [17].

Immune checkpoint inhibitors differ in their molecular targets, clinical approval status, and therapeutic indications in hepatocellular carcinoma. Table 2 summarizes the most relevant agents currently used or under investigation in clinical practice, along with their mechanisms of action and main clinical findings. Data derived from clinical trials and reviews referenced above.

Table 2. Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Targets and Clinical Evidence

Inhibitor	Molecular Target	Approval Status	Key Study / Indication	Notes on Efficacy and Safety
Nivolumab	PD-1	FDA-approved (2nd line)	CheckMate 040	Median response 17 mo; ORR linked to PD-L1 expression
Pembrolizumab	PD-1	Initially accelerated (2nd)	KEYNOTE trials	ORR 17%, mOS 12.9 mo; IrAEs in 14%
Atezolizumab	PD-L1	FDA-approved (1st line)	IMbrave150 (with bevacizumab)	Reduced OS risk by 56%; PFS by 40%
Durvalumab	PD-L1	NCCN guideline inclusion	Evaluated as monotherapy	Recommended for 1st line by NCCN
Tremelimumab	CTLA-4	Investigational	Clinical trial (2013)	PR 17.6%, DCR 76.4%; grade ≥3 AE: ↑AST, ↑ALT

Ipilimumab	CTLA-4	FDA-approved (melanoma)	Mentioned as CTLA-4 class representative	Used in HCC in combination regimens (off-label)

COMBINATION THERAPY

Recent clinical trials have shown that combination therapies that target both immune checkpoints and tyrosine kinase pathways are more effective than treatment with sorafenib alone in patients with advanced hepatocellular carcinoma (HCC) [6]. The combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) has shown synergistic anti-tumor activity [7]. Blockade of both VEGF/VEGFR and PD-1/PD-L1 acts at different levels in the tumor microenvironment to improve the immune response. In TME, interactions between tumor blood vessels and immune cells that promote tumor growth can interfere with the immune response, promoting disease progression and undermining the effectiveness of therapy. Abnormal tumor neovascularization produces an endothelial barrier, limiting T-cell infiltration, which enables the tumor to evade the immune response and promotes angiogenesis [11]. Studies have shown that pro-angiogenic factors, such as VEGF, can induce T-cell depletion, which promotes tumor evasion of the immune response [25,27]. VEGF is a key factor in tumor angiogenesis, and resistance to immunotherapy is more pronounced in tumors with high levels of VEGF. Thus, interactions between angiogenesis and tumor resistance suggest that improving tumor vascular structure may enhance the efficacy of anti-PD-1 immunotherapy. In addition, vascular normalization may promote tumor infiltration by T cells after immunotherapy [11]. This combination of VEGF inhibitors and anti-PD-1/PD-L1 therapy is a reasonable treatment strategy [25]. Compared to sorafenib treatment, combination therapy improved median overall survival (mOS) to 19.2 months (versus 13.4 months in the sorafenib group), as well as median progression-free survival (mPFS) to 6.8 months (versus 4.3 months), with an overall response rate (ORR) of 30% (versus 11% in the sorafenib group) [25]. The safety of combination therapy was not significantly different from that of sorafenib, with 61.1% of patients experiencing grade 3 or higher side effects, and 15.5% having to discontinue treatment due to side effects. In contrast, 60.9% of patients in the sorafenib group experienced grade 3 or higher side effects, and 10.3% had to discontinue treatment. In 2020, based on the results of the IMbrave150 trial, the combination of atezolizumab and bevacizumab was approved by the FDA as a first-line treatment for advanced HCC [18,28], setting a new standard of treatment for patients who had not been treated before. The combination yields a twofold increase in response rates, with approximately 5% complete remissions and long survival times exceeding 18 months [9].

IMMUNE-MEDIATED ADVERSE EVENTS

Immune checkpoint molecules play a key role in maintaining immune balance. Inhibitory molecules such as PD-1 and CTLA-4 are particularly important for regulating T-cell activation and maintaining self-tolerance [4]. Immunotherapy-related adverse reactions (IrAEs) can affect a variety of organ systems and include everything from mild rashes to serious, life-threatening side effects. IrAEs caused by PD-1/PD-L1 inhibitors are dose-independent. The most commonly affected organs for anti-CTLA-4 and PD-1/PD-L1 inhibitors were the skin and gastrointestinal tract, while reactions in the endocrine system and liver were observed less frequently. In a meta-analysis of phase 2/3 trials in patients using checkpoint inhibitors, rash appeared to be the most common IrAE, while colitis and aspartate aminotransferase elevation were the most common severe IrAEs. Ipilimumab was associated with a higher incidence of rash and colitis than anti-PD-1/PD-L1 drugs. Cutaneous IrAEs can range from mild rashes and pruritus to more severe, rare cases such as Stevens-Johnson syndrome. For gastroenterologic IrAEs, especially colitis and/or diarrhea, differential diagnosis is important to rule out infectious disorders and side effects of other medications. The diagnosis of immune-mediated hepatitis in HCC patients undergoing ICI therapy is difficult, requiring exclusion of tumor growth in the liver, viral hepatitis B or C, cytomegalovirus reactivation, drug toxicities, or ascites, among others. If necessary, a liver biopsy is considered before starting steroid treatment. In severe cases, oral or intravenous steroids are used. Pneumonia, a serious IrAE, requires prompt differential diagnosis, including exclusion of viral causes, hepatopulmonary syndrome, and portal-pulmonary hypertension. Thyroid-related adverse reactions include both hypothyroidism and hyperthyroidism, caused by inflammation of the gland [4,29]. With dual blockade of CTLA-4 and PD-1, hepatic adverse reactions appear after 4-5 weeks of therapy, and about 90% of cases resolve after 6-8 weeks [9]. IrAEs are often difficult to predict and can affect a variety of organs, but in general, checkpoint inhibitors are better tolerated than multidirectional kinase inhibitors. As shown in the phase III CheckMate 459 study, nivolumab, compared to sorafenib, was associated with lower rates of severe adverse events (TRAEs; 22% vs. 49%) and improved health-related quality of life [22,30]. Given the complexity of hepatocellular carcinoma and the evolving role of immunotherapy, particularly immune checkpoint inhibition, the growing body of evidence highlights the need to synthesize current findings, evaluate clinical implications, and define priorities for future research and practice.

CONCLUSIONS

Hepatocellular carcinoma (HCC) remains one of the most lethal cancers due to late-stage diagnosis and limited curative options. In addition to viral hepatitis and cirrhosis, metabolic disorders such as obesity, type 2 diabetes, and NAFLD have become key risk factors, underscoring the need for improved screening strategies.

Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have expanded treatment options in advanced HCC. Combination regimens, notably atezolizumab with bevacizumab, offer clinical benefit, though durable responses remain limited. Tumor heterogeneity and immune evasion continue to hinder efficacy.

Future progress depends on identifying predictive biomarkers, optimizing therapy sequencing, and expanding early detection programs to include metabolic risk groups. Although limited by its narrative scope, this review outlines current evidence with a focus on immunotherapy.

RECOMMENDATIONS

Expand surveillance to include patients with metabolic risk factors alongside those with viral hepatitis and cirrhosis.

Promote early detection through imaging and biomarkers in high-risk populations.

Use immune checkpoint inhibitors, particularly atezolizumab with bevacizumab, in eligible patients with advanced HCC.

Monitor responses closely due to limited efficacy and potential progression.

Support research on resistance mechanisms and combination strategies to improve outcomes.

Despite recent advances, improving HCC outcomes will require earlier diagnosis, refined patient selection, and continued development of more effective treatment combinations.

DISCLOSURES

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, software check, formal analysis: Paulina Redel

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USE OF AI

Artificial intelligence tools (e.g., ChatGPT, OpenAI) were used to assist with language editing, structural refinement, and the formulation of selected textual segments (e.g., background synthesis, objectives, conclusions). All AI-assisted content was critically reviewed, fact-checked, and finalized by the authors.

CONFLICTS OF INTEREST

Authors have no conflict of interest to declare.

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back