Hepatocellular Carcinoma: An Update

Author

Hubert E. Blum

Affiliation

University Hospital Freiburg, Department of Internal Medicine II, Hugstetter Strasse 55, D-79106 Freiburg, Germany

Correspondence
Hubert E. Blum, MD
Department of Internal Medicine II
University of Freiburg
D-79106 Freiburg, Germany
E.Mail: hubert.blum@uniklinik-freiburg.de
Telephone: +49-761-270-18116
Fax: +49-761-270-18117

Abstract

Hepatocellular carcinoma is one of the most common malignant tumors worldwide. The major etiologies and risk factors for the development of HCC are well defined and some of the multiple steps involved in the clincal and molecular hepatocarcinogenesis have been elucidated in recent years. Despite these scientific advances and the implementation of measures for the early detection of HCC in patients at risk, patient survival has not significantly improved during the last three decades. This is due to the advanced stage of the disease at the time of clinical presentation and the limited therapeutic options. The therapeutic options fall into several categories: (i) surgical interventions including tumor resection and liver transplantation, (ii) percutaneous interventions, including ethanol injection and radiofrequency thermal ablation, (iii) transarterial interventions including embolization, chemoembolization and selective internal radiotherapy, (iv) external radiation therapy and (v) systemic strategies with cytotoxic agents and molecularly targeted therapies as well as immunotherapies.

These therapeutic strategies have been evaluated in part in randomized controlled clinical trials that are the basis for the current therapeutic recommendations. While surgery, percutaneous and transarterial interventions are effective in patients with limited disease (1-3 lesions, <5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis more than 80% of patients present with multicentric HCC and advanced liver disease or comorbidities that restrict the therapeutic measures to best supportive care. In order to reduce the morbidity and mortality from HCC, early diagnosis and the development of novel systemic therapies for advanced disease, including cytotoxic agents, molecular targeted and immunotherapies is most important. New analytical technologies, including gene expression profiling, proteomic analyses and others, should allow to further elucidate the molecular events underlying HCC development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

Keywords: HCC resection, liver transplantation, percutaneous ethanol injection, radiofrequency thermal ablation, transarterial embolization or chemoembolization, radiation therapy, systemic chemotherapy, molecular targeted therapy, immunotherapy, prevention

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide [1]; [2]. Up to now HCCs are caused in most cases by chronic HBV or HCV infection as well as alcohol abuse. Universal HBV vaccination as well as the wide implementation of direct acting antiviral agents (DAAs) against HCV infection clearly are changing the etiologic landscape to nonalcoholic fatty liver disease (NAFLD) together with metabolic syndrome and obesity that are becoming the leading causes of liver diseases in Western countries [3].

Epidemiology

HCC is the fourth leading cause of cancer-related mortality worldwide with an estimated deaths of 1 million patients in 2030 (World Health Organization. Projections of mortality and causes of death 2016 to 2060.http://www.who.int/healthinfo/global_burden_disease/projections/en/). With a 5-year survival of only 18% it is the second most lethal tumor after pancreatic cancer. Men are 3 times more frequently affected than women [4]. The worldwide incidence varies according geographic region: about 70% occur in Asia, 10% in Europe and about 5% in Africa, North America and Latin America, respectively. While chronic HBV and HCV infection as well as alcohol abuse (**Table 1**) are currently the major underlying causes of liver disease, after the wide implementation of universal HBV vaccination and the successful DAA treatment of HCV infection, NAFLD, metabolic syndrome and obesity are expected to become the leading cause of HCCs. Apart from the prevention or effective treatment of the underlying liver disease, statins [5], aspirin [6], metformin [7] and caffeinated and decaffeinated coffee can reduce the HCC risk [8] [9]. In addition to the above mentioned risk factors there are several inherited disorders that are associated with HCC development, such as iron overload, alpha-1 antitrypsin deficiency, acute intermittent porphyria and others.

Table 1: HCC etiologies

HBV infection, esp. in combination with aflatoxin B_1 exposure
(Asia and sub-Saharan Africa)
HCV infection (Western countries and Japan)
HIV coinfection with HBV and HCV
Alcoholic liver disease
Non-alcoholic fatty liver disease (NAFLD)
Metabolic syndrome
Obesity
Smoking
Genetic susceptibility, such as iron overload, alpha-1 antitrypsin deficiency, acute intermittent porphyria and others

Molecular Pathogenesis

The major etiologies of HCCs are well defined and result in chronic hepatic inflammation, fibrosis and aberrant hepatic regeneration. As for most types of cancer, hepatocarcinogenesis is a multistep process involving different genetic and epigenetic alterations that ultimately lead to the malignant transformation of hepatocytes. The most frequent genetic alterations are mutations in the TERT promotor, the cell cycle, WNT signaling and chromatin remodeling. Interestingly, no defined mutation has been detected to date that predicts a therapeutic response, different from other forms of cancer. Further, the tumor microenvironment appears to play a key role in tumor progression. Most HCCs occur after many years of chronic hepatitis that provides the mitogenic and mutagenic environments to precipitate random genetic alterations resulting in the malignant transformation of hepatocytes and HCC development.

The HCC risk in patients with liver cirrhosis depends on the activity, duration and etiology of the underlying liver disease. Clinical and biological variables (age, anti-HCV positivity, PTT and platelet count) allow to further identify a subset of cirrhotic patients with the highest risk of HCC development. On the other hand, there is evidence that HBV and possibly HCV under certain circumstances play an additional direct role in the molecular pathogenesis of HCC. Finally, aflatoxins can induce mutations of the p53 tumor suppressor gene, thus pointing to the contribution of an environmental factor to tumor development at the molecular level. Furthermore, in a transgenic mouse model it has been shown that chronic immune-mediated liver cell injury without environmental or infectious agents is sufficient to cause HCC and that inhibition of cytotoxic T lymphocyte-induced apoptosis and chronic inflammation by neutralization of the Fas ligand can prevent HCC development in this model. In addition, in another transgenic mouse model it has been demonstrated that NF-κB may be the link between inflammation and HCC development. Finally, individual polymorphisms of drug-metabolizing enzymes, such as cytochrome P450 oxidases, N-acetyltransferases and glutathione-*S*-transferase, may contribute to the genetic susceptibility to HCC development.

Diagnosis and surveillance

HCC detection in patients with chronic liver disease/ cirrhosis is based on ultrasonography examinations every 6 months [10] or after 12 months if the lesion is stable in size. Contrast-enhanced ultrasound is not recommended because it does not differentiate HCC from cholangiocarcinoma. Complementary and frequently definitive imaging techniques are CT and MRI with hyperenhancement in the arterial and washout in the venous phase. In case of inconclusive patterns diagnosis should rely on biopsy, possibly including immunostaining for glypigan 3, heat shock protein 70, glutamine synthetase, clathrin heavy chain and others. The detection of HCC-specific mutations in circulating tumor cells (liquid biopsies) is not yet established to date.

The most common HCC serum marker is alpha-fetoprotein (AFP). It also can be elevated in pregnancy, with tumors of gonodal origin, and a variety of other tumors, especially gastric cancer. Plasma microRNAs (miR-122, 192, -21, -223, -26a, -801) have also been studied as possible HCC markers, in part with positive results. Further, other serum markers alone or in combination with AFP, such as glypican-3, des-gamma-carboxy-prothrombin, lens culinaris agglutinin-reactive AFP have been evaluated. None of these markers can yet be recommended for routine clinical use, however.

Staging and prognostic assessment

For the staging of HCCs, numerous systems have been proposed. Among others, these are the Okuda staging system, the TNM classification and its modification by the Union International Contre Cancer (UICC), the Barcelona Clinic Liver Cancer (BCLC) classification and the Cancer of the Liver Italian Program (CLIP) score. The BCLC staging system has been extensively validated and is clinically most important for the appropriate choice of the therapeutic strategy for individual patients. BCLC defines 5 stages (0 - D), based on liver function, Eastern Cooperative Oncology Group performance status (ECOG-PS) and tumor burden. The 5 stages are:

I. **Very early stage 0**: preserved liver function, ECOG-PS 0, 1 lesion <2 cm;

II. **Early stage A**: preserved liver function, ECOG-PS 0, 1 lesion >2 cm or 2-3 lesions, all <3 cm;

III. **Intermediate stage B**: preserved liver function, ECOG-PS 0, multiple lesions (3, >2 if any >3 cm);

IV. **Advanced stage C**: preserved liver function, ECOG-PS 1-2, macrovascular invasion or extrahepatic lesion;

V. **Terminal stage D**: end-stage liver function, ECOG-PS <2, non-transplantable HC

Treatment strategies

The aim of the treatment is an increase of patient survival and maintaining a high quality of life. Strategies for HCC therapy depend on the stage of the tumor and can be divided into different categories (**Table 2**): surgical interventions, percutaneous or transarterial loco-regional therapies and systemic treatment modalities. It is of paramount importance to select the most appropriate treatment strategy and its expert application.

Table 2: Stage-adapted HCC therapy

Stage	Treatment	Survival
(0) Very early: single lesion, <2 cm	**see (A)**	**>5 yrs**
(A) Early: 1 lesion >2 cm or 2-3 lesions, all <3 cm	**Resection Transplantation or Ablation**	**>5 yrs**
(B) Intermediate: multiple nodules	**Chemoembolization**	**>2.5 yrs**
(C) Advanced: portal invasion, extrahepatic spread	**Systemic**	**ca. 1 yr**
(D) Terminal: end-stage liver function	**Best supp. care**	**ca. 3 mo.**

Surgical interventions. The ideal candidates for resection are patients with HCC BLCL stage 0 or A. These patients have a **r**esection-related mortality of <1-3% and a 5-year survival rate of >60%. However, as many as 70% of these patients have a tumor recurrence at 5 years [11]. Unfortunately, to date there are no effective adjuvant therapies established to reduce recurrence after resection [12]. Therefore, strategies aimed at secondary HCC prevention are of paramount importance (see below).

Liver transplantation is in principle the optimal therapeutic option for HCCs, because it simultaneously removes the tumor and the underlying cirrhosis, including the risk of HCC recurrence. The current criteria for liver transplantation in patients with HCC (1 lesion <5 cm in diameter or maximum 3 lesions <3 cm in diameter) result in a 5-year survival rate of 60-80% and of 50% at 10 years and a recurrence rate of <15%. Possibly, these criteria can be extended in the future, depending on more experiences based on the stage of the disease, macrovascular invasion, histopathological characteristics (histopathology, aneuploidy, microvascular invasion) as well as DNA and RNA chip data (molecular signature, proteomic signature and others).

Clinically, it is most important to shorten the waiting time for liver transplantation to <6 months. This is difficult to achieve with cadaveric liver transplants due to the shortage of donors. With a waiting time of >12 months in some Western countries, the drop-out rate of patients is 20-50%. To bridge the time to transplantation and to prevent tumor progression, neoadjuvant treatments, such as percutaneous and transarterial interventions may lead to an improved outcome. Living donor liver transplantation has been shown to be an alternative to cadaveric liver trans-plantation. However, a very careful selection of patients and donors, including consideration of ethical, societal and legal issues is central to the successful implementation of living donor liver transplantation for the treatment of HCC patients.

Percutaneous loco-regional therapies. Percutaneous interventions are the best options for small unresectable HCCs. Tumor ablation can be achieved chemically by percutaneous ethanol injection (PEI) or acetic acid injection (PAI) or thermally by radiofrequency thermal ablation (RFTA), microwave heat-induced thermotherapy (HITT), laser-induced thermotherapy (LITT), high-intensity focused ultrasound (HIFU) or cryoablation. Apart from the percutaneous approach, these techniques can be applied also laparoscopically or after laparotomy. It is recommended for patients with BCLC stage 0 or A [10]. PEI is one of the most widely used techniques. It is safe, easy to perform, inexpensive and can achieve complete tumor response rate of 90-100% in HCCs <2 cm in diameter, 70% in HCCs <3 cm in diameter and 50% in HCCs <5 cm in diameter. Patients with liver cirrhosis Child A with complete responses can achieve a 5-year survival rate of 50% or more. Therefore, PEI is the procedure of choice for patients with a single HCC lesion <5 cm in diameter or with up to three lesions <3 cm in diameter. RFTA is an alternative to PEI. The efficacy of RFTA is similar to that of PEI and requires generally only a single intervention. RFTA offers a better local tumor control than PEI and has the potential advantage of allowing the ablation of tumors >5 cm in diameter especially when newer generation devices are used. However, the 5-year survival rate after complete response to RFTA is currently similar to that of PEI depending on the Child stage of the underlying liver cirrhosis. Thus, percutaneous HCC ablation by PEI or RFTA when considered together is an effective treatment for patients with HCCs that prolongs the tumor-free and overall survival time, especially if surgery is not feasible.

Transarterial loco-regional therapies. Transarterial embolization and transarterial chemoembolization (TACE) are the most widely used treatments for intermediate-stage HCCs (BLCL stage B). Embolization agents may be administered alone (embolization) or after intraarterial infusion of a cytotoxic agent (chemoembolization). A systematic review of TACE showed an objective response of 52.5% [13] with an associated mortality <1%. While TACE with dug-eluting beads has fewer side effects but similar efficacy than conventional TACE, embolization alone is controversial. Median survival after TACE ranges from 26-40 months.

Another transarterial intervention for patients with HCC BLCL stage B is selective internal radiation therapy (SIRT). It is based on the intraarterial infusion of Yttrium-90 microspheres without embolization that is safe and has a response similar to TACE in cohort and retrospective studies [14]. However, no improvement of survival was observed in patients with more advanced disease.

External beam radiation therapy. Intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) as well as proton beam therapy of HCCs are in the stage of clinical evaluation and have not yet reached a wider clinical application to date.

Systemic therapies. Systemic, palliative therapies are recommended for patients with HCC BLCL stage C and for patients with BLCL stage B who show a disease progress with transarterial therapies.

HCC must be considererd largely resistant to conventional cytotoxic chemotherapy and hormonal compounds, such as tamoxifen and antiandrogens, possibly due to the high rate of expression of multiple drug resistance genes.

In 2008, sorafenib, an oral molecularly targeted multikinase inhibitor that blocks RAF signalling, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and KIT showed in the Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial a median survival benefit of 10.7 months *versus* 7.9 months of the placebo group [15]. It was the first systemic drug approved by the Food and Drug Administration (FDA) for HCC treatment. It is more effective in Western patients as compared to patients from Asia. Many other agents were subsequently tested in phase 3 trials without significantly improving patient outcome [1 2].

More recently, lenvatinib, another multikinase inhibitor, targeted against VEGFR-1, -2 and -3, fibroblast growth factor receptors 1-4, PDGFR alpha and KIT, was approved by the FDA in 2017 for the treatment of HCCs [16] Regorafenib, another multikinase inhibitor, also increased survival in patients with tumor progression during sorafenib treatment and was the first drug approved by the FDA for second-line treatment [17]. Further, cabozantinib, also a receptor kinase inhibitor [18], and ramucirumab, an antibody against VEGFR-2, improve survival of HCC patients with elevated AFP levels [19]. Checkpoint inhibitor immunotherapy is an emerging therapeutic option for patients with advanced HCC, primarily as second-line treatment. The programmed cell death 1 (PD-1) immune checkpoint inhibitors nivolumab and pembrolizumab and the inhibitor of the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) ipilimumab have been evaluated in patients with HCC. The combination of nivolumab and ipilimumab was approved in March 2020 for HCC patients pretreated with sorafenib (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma).

Very recently, the combination of atezolizumab, a programmed cell death ligand 1 (PD-L1) inhibitor and bevacizumab (a monoclonal antibody targeting VEGF) showed as first-line therapy an improved survival as compared to sorafenib [20] [21]. Also, nivolumab was shown in the CheckMate-459-study to be superior to sorafenib as first-line therapy.

Systemic chemotherapy

Many patients worldwide may not have access to one of the stage-adapted therapies detailed above. In these patients wider available, less expensive systemic chemotherapies remain an option: gemcitabine plus oxaliplatin, gemcitabine plus pegylated liposomal doxorubicin or capecitabine monotherapy. Capecitabine monotherapy may be an option for patients with advanced disease or with jaundice.

Primary and secondary prevention

Clinically, preventive strategies are of paramount importance as primary prevention, e.g., vaccination against hepatitis B or elimination of hepatitis C as well as the effective treatment of patients infected with HBV and/ or HCV. In view of the high recurrence rate in treated HCC patients secondary prevention is also of high priority.

Summary and perspectives

HCC is one of the most common malignant tumors in some areas of the world with a poor prognosis. HCC treatment is based on randomized controlled trials and observational studies of stage-adapted treatment modalities. Treatment options fall into several categories: surgical interventions, including tumor resection and liver transplantation, percutaneous interventions including ethanol injection and RFTA, transarterial interventions, including embolization and TACE, radiation strategies and systemic therapies. While surgery as well as percutaneous and transarterial interventions are effective in patients with limited disease (up to three lesions <3 cm in diameter or one lesion <5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis more than 80% patients present with multicentric HCC and advanced liver disease or comorbidities that restrict the therapeutic measures to BSC.

In order to reduce the morbidity and mortality of HCC, early diagnosis and the development of novel systemic therapies for advanced disease, including moleculary targeted drugs and immunotherapies as well as primary HCC prevention are of paramount importance. Furthermore, secondary HCC prevention after successful therapeutic interventions needs to be improved in order to achieve a better long-term survival of HCC patients. New technologies, including gene expression profiling and proteomic analyses, should allow to further elucidate the molecular events underlying HCC development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

Acknowledgement. The excellent secretarial assistance of Mrs. M. Gutgsell is gratefully acknowledged.

No conflict of interest.

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet.* 2018;391(10127):1301-1314.
2. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med.* 2019;380(15):1450-1462.
3. Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol.* 2019;17(4):748-755 e743.
4. Global Burden of Disease Liver Cancer C, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol.* 2017;3(12):1683-1691.
5. Kim G, Jang SY, Nam CM, Kang ES. Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study. *J Hepatol.* 2018;68(3):476-484.
6. Simon TG, Ma Y, Ludvigsson JF, et al. Association between aspirin use and risk of hepatocellular carcinoma. *JAMA Oncol.* 2018;4(12):1683-1690.
7. Tseng CH. Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. *Liver Int.* 2018;38(11):2018-2027.
8. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open.* 2017;7(5):e013739.
9. van Dam RM, Hu FB, Willett WC. Coffee, caffeine, and health. *N Engl J Med.* 2020;383(4):369-378.
10. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the Liver. EASL Clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236.
11. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology.* 2008;134(7):1908-1916.
12. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2015;16(13):1344-1354.
13. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. *Hepatology.* 2016;64(1):106-116.
14. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2016;151(6):1155-1163 e1152.
15. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.
16. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet.* 2018;391(10126):1163-1173.
17. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10064):56-66.
18. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing

hepatocellular carcinoma. *N Engl J Med.* 2018;379(1):54-63.
19. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(2):282-296.
20. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med.* 2020;382(20):1894-1905.
21. Kelley RK. Atezolizumab plus bevacizumab - A landmark in liver cancer. *N Engl J Med.* 2020;382(20):1953-1955.