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Hepatocellular Carcinoma: A Review

Stoian Marilena[1], Indrei Lucia[2] and Stoica Victor[2]

[1]Internal Medicine Department, Carol Davila University of Medicine and Pharmacy, Bucharest
[2]Internal Medicine Department, Dr. Ion Cantacuzino Clinical Hospital, Bucharest

Abstract

Hepatocellular carcinoma is amongst the leading causes of cancer deaths globally, and its incidence is rising not only in Europe, but worldwide, despite the fact that it is preventable, due to the comprehensive understanding of risk factors and underlying liver disease contributing to carcinogenesis. In this paper we present the latest recommendations regarding prevention strategies and screening programs, diagnostic techniques, staging systems and the optimal treatment options for each evolutional stage, with a glimpse into the future directions of the systemic treatment of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, Thermal ablation, Transarterial chemoembolization, Immune therapy

Introduction

Hepatocellular Carcinoma (HCC) accounts for more than 90% of primary liver cancers, the second most frequent cause of cancer-related death [1]. Although technically any cirrhosis, regardless of its etiology, may be complicated by a malignant tumor development, it is generally accepted that the risk is greater for patients with chronic viral hepatitis, for whom the metabolic syndrome represents an additive risk factor [2,3]. Another frequent risk factor is the alcoholic liver disease and lately the prevalence of HCC amongst the patients with non-alcoholic fatty liver disease (NAFLD) in association with metabolic syndrome has been on the rise, with the possibility of developing HCC even in the absence of cirrhosis [4].

Prevention and screening

The World Health Organization recommends the vaccination against hepatitis B for all new-borns (even in low-endemic areas) and for the people at high risk of contracting the infection (i.e. IV drug users, health care workers, travelers to endemic areas). Interferon, tenofovir, lamivudine and entecavir have proved useful in the secondary prevention of HCC in patients with chronic hepatitis B, especially associated with cirrhosis [5]. For patients with chronic hepatitis C there was a significant risk reduction of HCC after obtaining a sustained virologic response (SVR) with interferon [6], while controversy persists regarding the role of direct-acting antivirals (DAA). Some authors suggest that the risk of occurrence or recurrence of HCC is higher in patients treated with DAA compared to interferon, with potentially more aggressive tumors in recurrent HCC [7,8] However, a recent meta-analysis did not find any significant difference between interferon and DAA [9], while a retrospective cohort study proved a reduced incidence of HCC in patients who achieved SVR with DAA [10]. There is evidence that coffee reduces not only the incidence of HCC, but also the overall mortality associated with chronic liver disease, although there is no clear dose recommendation [11].

EASL strongly recommends the periodic surveillance of cirrhotic patients (Child-Pugh stages A and B, and only those Child-Pugh stage C patients waiting for a liver transplant), using abdominal ultrasound every six months [2,12,13]. Based on individual risk factors, non-cirrhotic patients with NAFLD may be considered candidates for screening.

Diagnosis

In cirrhotic patients with high probability of HCC, the diagnosis can be established only based on non-invasive imagistic criteria: arterial phase hyper-enhancement (APHE) with washout in the portal venous phase on CT or MRI, only for nodules ≥1 cm [14,15]. When CT and MRI are inconclusive, a contrast enhanced ultrasonography (CEUS) showing APHE followed by a mild and late (≥60 seconds) washout is suggestive for HCC [16].

Liver biopsy and histopathological confirmation are mandatory for the HCC diagnosis in non-cirrhotic patients, as well as in cirrhotic patients with inconclusive imaging, remaining the gold standard for defining HCC and the differential diagnosis with other primary liver malignancies (intrahepatic cholangiocarcinoma, combined hepatocellular carcinoma/cholangiocarcinoma) [2]. Immunohistochemistry staining with a three-marker panel (GS, GPC3 and HSP70) can be used to support the diagnosis of early and well-differentiated HCC [17], while a positive stain for CK19 is associated with a poor prognosis [18]. The potential risks associated with liver biopsy, namely tumor seeding (2.7%), minor hemorrhage (3-4%) or severe hemorrhage requiring transfusion (0.5%), do not affect the course of the disease or the overall survival, are manageable and infrequent, and consequently do not represent a reason to refrain from performing the biopsy [2,19,20].

Histopathology: Precursor lesions

Hepatocellular adenoma (HCA) – although the typical adenoma-carcinoma sequence is rarely encountered in HCCs, some HCAs may act as precursor lesions. It appears that a higher risk of malignant transformation is associated with an activating beta-catenin mutation [21]. The evolution of HCA towards HCC is more frequently described in males undergoing androgen treatment or with glycogen storage diseases and in females with oral contraceptive treatment [22]. The differential diagnosis between well-differentiated HCC in noncirrhotic liver and HCA is particularly difficult when the β-catenin-activated hepatocellular adenoma like-tumor occurs in unusual clinical settings (unusual sex or age, i.e. men regardless of age or elderly women, as typical HCA is characteristic for young women) or presents an atypical focal architectural or cytological atypia – these tumors are classified

***Corresponding author:** Marilena Stoian, Internal Medicine Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, Tel: +400733937310, E-mail: marilenastoian@yahoo.com

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as atypical hepatocellular neoplasm (AHN). There is evidence that in AHN with β-catenin activation there are both morphologic and cytogenetic changes typical for HCCs [23], suggesting that these tumors are actually at least borderline lesions, if not a very highly-differentiated type of HCC, hence the recommendation for tumor resection.

Dysplastic foci – clusters smaller than 1 mm of atypical cells in respect of nuclear size, cytoplasmatic staining or cellular morphology (including the small cell dysplasia typically encountered in cirrhotic livers), but do not meet the criteria for malignancy, lacking the invasive growth [24].

Dysplastic nodules – lesions larger than 1 mm, usually associated with cirrhosis, which can progress to HCC or also regress. Based on their characteristics, dysplastic nodules can be divided into low-grade and respectively high-grade. Low-grade dysplastic nodules do not present any mitoses, show only minimal atypia and normal or just minimally increased nuclear/cytoplasmatic ratio, with the preservation of the reticulin network and portal tracts. The high-grade dysplastic nodules are characterized by occasional mitoses, peripherally located hyperchromatic nucleus with irregular borders and an increased nuclear/cytoplasmatic ration, basophilic cytoplasm, and occasionally pseudo glandular pattern or unpaired arteries (from which the dysplastic nodules may derive their blood supply) [25,26]. Other cell atypia suggestive changes that can help distinguish high-grade dysplastic nodules from the low-grade ones are focal fatty change (with Mallory-Denk bodies), clear cell change and resistance to iron accumulation.

Macroscopy of HCC

HCCs are typically softer than the surrounding tissue, presenting often a pseudocapsule of fibrous tissue in cirrhotic livers, while in noncirrhotic settings the tumors tend to be unencapsulated. Unifocality and multifocality play an important part in prognosis and the choice of the best therapeutic option. Most of the unifocal HCCs arise from equivocal preexistent nodular lesions, and are usually well-differentiated at early stages, with the possible multistep evolution to advanced and poorly-differentiated HCCs, especially in patients with chronic HBV or HCV hepatitis [27]. Multifocality is described as tumor nodules which are clearly separated by non-neoplastic liver. The multifocal tumors represent either simultaneously arising independent HCCs known as multicentric HCCs (frequently seen in chronic HBV infections, where the genetic changes induced by the HBV integration patterns are responsible for the independent development of multicentric malignant nodules [28,29]) or intrahepatic metastases from a primary tumor known as satellite tumor nodules. These two distinct possibilities reflect different pathogenic pathways, of utmost importance for treatment and prognosis, as intrahepatic metastases tend to be more often poorly differentiated and more aggressive.

HCCs can be divided into early HCCs (well differentiated, size < 2 cm and vaguely nodular type – poorly defined margins to the surrounding liver) and progressed HCCs (> 2 cm, or size < 2 cm, but moderately differentiated, distinctly nodular type – presents a discernible capsule), according to WHO and international consensus group for hepatocellular carcinoma [30,31]. Macroscopically, progressed HCCs can be nodular, massive or diffuse. The nodular type may comprise a singular encapsulated nodule with or without extracapsular growth adjacent to the nodule or an aggregation of differently sized nodules. The term massive type is generally used to describe a large dominant mass with irregular demarcation with or without smaller satellite nodules, an aspect also encountered in advanced nodular HCC. Diffuse or cirrhotomimetic type is a rare HCC growth pattern characterized by numerous small tumor nodules disseminated throughout the whole liver, closely mimicking the cirrhotic regenerative nodules [25].

Pedunculated HCCs are tumor masses protruding outside the liver with or without a pedicle (some authors use the term protruding HCC if the peduncle is absent). Initially a good prognosis was reported for this type of tumor, although not all the studies have confirmed this outcome [32,33].

Macroscopic findings may be affected by varying grades of portal vein involvement or tumor necrosis, by the accumulation of cytoplasmic glycogen or by the production of bile or fat.

Histopathology of classical HCC

The conventional HCC comprises tumor cells generally resembling hepatocytes, but with cytological atypia and mitotic activity or vascular invasion and stroma consisting of sinusoid-like blood spaces. The endothelial cells of HCC demonstrate changes of "capillarization", as ultrastructural studies have proven the existence of a basement-membrane-like structure interposed between the trabeculae of tumor cells and the endothelial cells. The angioarchitecture is crucial not only for tumor growth, but also for the imaging techniques. Progressed HCCs are characterized by a prominent neovascularization through unpaired arteries (positive for SMA and CD34 and a smaller amount of elastic fibers than normal intrahepatic arteries), thus appearing hypervascular in imaging, in contrast with the hypovascular appearance of the early HCCs. Typically, there are no portal tracts in the HCC tissue, although they may be present in early HCCs or at the tumor periphery.

HCCs are highly variable from an architectural and cytological point of view, with different architectural patterns and cytological variants occurring frequently at the same patient depending on the different stages of tumor differentiation or in combination. From an immunohistochemmical point of view, around 90% of HCCs are positive for HepPar1 (cytoplasmic positivity with antibodies to carbamoyl phosphate synthetase-1).

The histologic classification of HCC

In addition to the classical or conventional HCC, the WHO admits the existence of 5 morphological subtypes: fibrolamellar HCC (FL-HCC), scirrhous HCC (S-HCC), undifferentiated carcinoma, lymphoepithelioma-like carcinoma and sarcomatoid HCC.

In matters of architectural pattern, HCCs usually present with the following: trabecular or plate-like pattern (most common in well-differentiated or moderate-differentiated HCCs, with trabeculae becoming progressively thicker with de-differentiation; this pattern can be more easily identified using CD34 immunostaining or a reticulin staining), pseudoglandular or acinar pattern (pseudoglandular structures are generally smaller in well-differentiated HCCs than in moderate-differentiated tumors, and their content is frequently PAS+) and compact pattern (usually encountered in poorly differentiated HCCs, where the slit-like sinusoid-like spaces provide the solid appearance of the tumor).

Cytological variants include: pleomorphic cells (typical for poorly differentiated HCCs, without a distinct trabecular pattern, with variably shaped and sized cells lacking cohesiveness, and frequent bizarre multinucleated and giant cells), clear cells (a well-differentiated type of HCC, with cells with a clear cytoplasm due to the accumulation of glycogen, sometimes making it hard to differentiate the HCC from a metastatic renal clear-cell carcinoma, requiring an IHC stain with

HepPar1 in order to establish the primary hepatic origin), fatty change (frequent in small, early-stage HCCs, its frequency being inversely proportional with the size of the tumor; probably a consequence of the insufficient blood supply in the initial stages of hepatocarcinogenesis), bile production (yellowish tumor, turning green after fixation with formalin), hyaline or Mallory-Denk bodies (usually irregular intracytoplasmatic eosinophilic and PAS- bodies, positive for antibodies to keratin and ubiquitin, consisting of aggregated intermediary filaments), pale bodies(typical for the fibrolamellar variant of HCC; round-ovoid eosinophilic amorphous material in the cystically dilated endoplasmic reticulum, positive for fibrinogen in IHC) and ground-glass inclusions (appearing in HCCs developed in HBsAg-positive patients) [31].

Special types of HCC

Fibrolamellar HCCs – These carcinomas tend to affect younger individuals, with a mean diagnostic age of 25 [34], arising in non-cirrhotic livers, with unknown etiology and risk factors, and with a prognosis similar to other HCCs in non-cirrhotic livers, better than classical HCC [35]. The defining histological features of fibrolamellar carcinoma consist of lamellar fibrosis encompassing large polygonal cells with oncocytic cytoplasm and large nuclei [5]. Although in many cases a central scar is present, suggesting a possible connection with focal nodular hyperplasia, these two lesions do not appear to be etiologically related. Focal CK19 and important CK7 expression was reported in this subtype of HCC [36].

Scirrhous HCC – the scirrhous growth pattern describes the prominent fibrosis alongside the sinusoid-like blood spaces, representing more than half of the tumor and encompassing small nests of tumor cells [37]. This histological aspect might be also noticed following transarterial chemoembolization, chemotherapy or radiation, but the post-therapeutic fibrosis needs to be distinguished from the scirrhous histologic subtype. Due to the abundant fibrotic changes of the tumor stroma, scirrhous HCC may closely resemble cholangiocarcinoma, both radiologically and pathologically, but the combination Glypican-3 (GPC-3) + Arginase-1 is useful in the differential diagnosis, having a100% sensitivity for scirrhous HCC [38]. Unlike other HCCs, scirrhous HCC is frequently positive for CK7, while the classical expression of HepPar1 is less common.

Undifferentiated carcinoma – tumors that can be diagnosed as primary carcinomas of the liver on an immunohistochemical basis, but cannot be further classified. They are considered to have a worse outcome compared to classical HCCs.

Lymphoepithelioma-like carcinoma – infrequent type of HCC, characterized by an abundant inflammatory infiltrate consisting mostly of lymphocytes (with the predominance of CD3+ CD4+ lymphocytic subtype), with only a few pleomorphic small tumor cells with focal syncytial growth (and in some cases positive for Epstein-Barr virus). Some authors suggest that this particular aspect might reflect a regression phenomenon [39].

Sarcomatoid HCC – characterized by spindle-shaped, bizarre, anaplastic tumor cells, sometimes hard to distinguish from leiomyosarcoma or fibrosarcoma, especially in the absence of adjacent classical HCC areas. Sarcomatoid changes are more frequently observed in the cases with multiple transarterial chemoembolization or chemotherapy [40].

Clear cell HCC – the defining cytoplasmic clearing is usually the result of glycogen, lipopolysaccharides, mucopolysaccharides or cytoplasmic vesicle accumulation. In order to be classified as a clear cell HCC, the tumor must contain at least 50% cells with clear cytoplasm.

Being a well-differentiated type of HCC, the prognosis of clear cell HCC is better or at least similar when compared to classical HCC [41]. Taking into consideration that there are very few cases of clear cell HCCs arising in hepatitis-free or non-cirrhotic livers [42,43], the presence of a tumor with clear cells within an otherwise normal liver architecture should raise the suspicion of a metastasis from another primary tumor with clear cells, most frequently a clear cell renal or ovarian carcinoma. Usually the HepPar1 expression is useful in distinguishing between a primary liver neoplasia and a metastatic process. However, some ovarian clear cell carcinomas are also positive for HepPar1 staining, making the differential diagnosis more challenging [44,45].

Steatohepatitic HCC – characterized by histological features seen in steatohepatitis representing more than 5% of the tumor, such as Mallory-Denk bodies, inflammation and pericellular fibrosis, ballooning of the hepatocytes and macrovesicular steatosis. A study reported that 63.6% of steatohepatitic HCCs presented with background NAFLD, thus stressing out a possible connection between NAFLD and this particular subtype of HCC [46,47] and consequently the role played by steatohepatitis in hepatocarcinogenesis. However, cases of steatohepatitic HCC have been reported also in the absence of background metabolic disease and non-alcoholic fatty liver disease [48]. The increasing incidence and prevalence of metabolic disease and NAFLD, particularly in western societies, together with the documented observation that HCCs associated with metabolic syndrome or NAFLD can develop even in non-cirrhotic liver, may lead to new recommendations for HCC screening programs [49,50]. The molecular pathway of carcinogenesis of the steatohepatitic HCCs is slightly different: the beta catenin pathway alteration is less frequent compared to classical HCC [51]. Immunohistochemically, steatohepatitic HCCs usually present a more intense staining for amyloid A and C- reactive protein, as well as the conventional staining for HCC (HSP-70, GS, GPC-3). It appears that the prognosis of steatohepatitic HCC is similar to the conventional type of HCC [52].

Staging

After the confirmation of the diagnosis, the next essential step in the management of HCC is to assess the prognosis and indicate the optimal treatment accordingly. There is quite a wide variety of staging systems based on different clinical prognostic factors, with different advantages and disadvantages depending on the statistical model, the study population or the treatment interventional hand [53]. EASL endorses the BCLC (Barcelona-Clinic Liver Cancer) classification (comprising variables regarding the liver function, tumor size and morphological characteristics, as well as the general health performance status), primarily due to the fact that it dynamically links the tumor stage and the treatment option [54].

According to the BCLC classification system, patients with very early stage or stage 0 (preserved liver function i.e. Child-Pugh A without ascites, single nodule less than 2 cm without vascular invasion or satellites, PS 0) can benefit from either ablation or resection and have a mean survival of more than 5 years. In early stage or stage A (preserved liver function, single or 2-3 nodules less than 3 cm, PS 0) the treatment options include resection, transplant and ablation, also with a survival over 5 years. Chemoembolization is best suited for the intermediate stage or stage C (preserved liver function, multinodular and unresectable tumors, PS 0), with a survival of more than 2.5 years. Systemic therapy is reserved for advanced stages i.e. stage C (preserved

liver function, but with extrahepatic spread or portal invasion, PS 1-2), with a mean survival a little over 10 months, while in the terminal stage or stage D (end-stage liver function, non-transplantable HCC, PS 3-4) the only option remains the best supportive care, with an estimated survival of approximately 3 months [22,55].

Treatment options

Potentially curative treatment options comprise liver resection, orthotopic liver transplantation and ablation. Although only the liver transplantation addresses both the HCC and the underlying cause and is associated with a benefit in disease-free survival, there was no evidence of its superiority over liver resection in terms of overall survival [56].

In non-cirrhotic patients with HCC liver resection (LR) is the mainstay of treatment, with excellent results and low risks, even in the case of extended resections [57]. However, in the presence of NAFLD, the conditions associated with the metabolic syndrome may negatively influence the outcome [58]. When deciding for a LR in a cirrhotic patient, one should carefully assess the liver function (usually using the Child-Pugh scoring system or MELD score), the presence of clinically relevant portal hypertension associated with the extent of hepatic resection and the estimated remnant hepatic volume respectively (using CT/MRI), and last but not least the patient's comorbidities and performance status [59]. Technically solitary tumors of any size can benefit from LR, but the outcome varies inversely with the tumor size, provided that a R0 resection can be achieved respecting the liver function-preservation principles [60]. Multinodular HCC does not represent a contraindication for LR, if the nodules fulfill the Milan criteria. Adjuvant therapy is currently not recommended, despite the 50-70% tumor recurrence rate within 5 years following surgery, representing either de novo tumors developed on the remnant cirrhotic liver (more often after 2 years) or true recurrences in the form of intrahepatic metastases (usually appearing earlier, in the first two years following surgery).

Orthotopic liver transplantation (OLT) is a first-line option in selected patients, HCC being the only accepted indication for solid organ transplantation in cancer [61]. The Milan criteria (single lesion ≤5 cm or ≤3 nodules each ≤3cm, without vascular or extrahepatic invasion – extrahepatic metastases and tumor vascular invasion are absolute contraindications for OLT) are currently considered the benchmark for selecting patients and comparing with other criteria [62]. Patients beyond Milan criteria might be considered for OLT in the event of a successful downstaging to within these criteria, or if they meet the more liberal University of California San Francisco (UCSF) criteria (single lesion ≤6.5 cm or ≤3 nodules with the largest tumor ≤4.5 cm and total tumor diameter ≤8 cm, without vascular or extrahepatic invasion) [63]. OLT is severely limited by the low availability of liver allografts, with no clear criteria for prioritizing the allocation of the graft for patients with HCC, although they should include at least the tumor response to treatment, the tumor burden and the waiting time. In order to minimize the risk of tumor progression beyond the Milan criteria and pre-OLT drop-out patients may benefit from "bridging therapies", such as resection, local ablation or transarterial chemoembolization [64].

Ablation therapies classically comprise radiofrequency ablation (RFA), microwave ablation (MWA) and percutaneous ethanol injection (PEI). Laser ablation, cryoablation and irreversible electroporation have also been proposed for local ablation in HCC. RFA is the gold standard of treatment for BCLC-0 and BCLC-A patients where surgery is not feasible. In terms of efficiency the outcomes of RFA in solitary HCC smaller than 2 cm are at least equal to those of surgery, the location of the tumor being one of the most important factors to consider when deciding between RFA and surgery (due to the "heat sink" effect, RFA is less effective in tumors located less than 1 cm away from a larger vessel i.e. more than 3 mm diameter) [65]. Taking into account the lesser morbidity and invasiveness and also the benefit of destructing the unidentified satellite tumors due to the extension of the ring of necrosis in the peritumoral tissue, RFA could be recommended as first-line treatment in BCLC-0 even when surgery is possible [66]. MWA has proved similar results in terms of local control and overall survival, with a study suggesting the superiority of MWA over RFA in larger tumors [66,67]. Moreover, due to the use of electromagnetic energy for thermal ablation, MWA is less affected by the "heat sink" effect. PEI is usually considered an alternative when thermal ablation is not technically feasible, mostly for tumors smaller than 2 cm, as in larger nodules the tumor necrosis is incomplete, leading to local recurrence in up to 49% of the cases [68,69]. Laser ablation and cryoablation are not inferior to RFA regarding overall survival, but laser ablation requires higher operator skills, while the benefits of cryoablation in local tumor progression are counterbalanced by the risk of "cryoshock" (severe coagulopathy and disseminated intravascular coagulation leading to multi-organ failure) [70-72].

Irreversible electroporation is a new technique that induces cell death by generating pores in the cell lipid bilayer through high-current electrical pulses, presenting the advantage of complete tumor necrosis while preserving the bile ducts in the target area. However, it requires general anesthesia, making it costlier and more demanding than RFA or MWA [73]. In all ablation techniques it is of utmost importance to assess the presence and volume of post-procedural tumor necrosis, using CT, MRI or CEUS.

Transarterial chemoembolization (TACE) is the first treatment option for selected patients with unresectable HCC, namely asymptomatic patients with a good performance status and uni- or pauci-nodular tumors – stage BCLC-B[33]. TACE can also be used in earlier stages if ablation, OLT or LR are not feasible, or as a bridge to transplant in order to minimize the drop-out risk. Tumor invasion of the main portal branches or impaired portal flow, as well as extrahepatic spread are absolute contraindications for the procedure [74]. The standard of practice still remains the lipiodol-based TACE, although there is evidence the TACE with drug-eluting beads (TACE-DEB) is associated with a reduced risk of systemic side effects (mainly cardiac toxicity) of chemotherapy due to the leakage of doxorubicin in the systemic circulation [75]. However, a retrospective study suggests the global hepatic and biliary injuries are more frequent with TACE-DEB [76]. Currently there is no clear recommendation regarding the duration and frequency of TACE treatment, but is generally accepted that aggressively repeated TACE procedures induce liver failure and that TACE should not be repeated if there is no substantial tumor necrosis after two sessions or in the event of untreatable progression[33]. Combining TACE with systemic anti-angiogenic agents is not recommended, but the association of TACE and RFA is beneficial especially for HCCs larger than 3 cm in terms of overall and disease-free survival [77].

The main indication for selective internal radiation therapy (SIRT) is the treatment of locally advanced HCC. In BCLC-B stage SIRT is associated with a better quality of life, improved tumor control and a longer time to progression and less toxicity (SIRT can be safely used even in the event of portal vein thrombosis [78]) when compared to TACE, but this does not translate into a benefit on overall survival

[79-81]. Similarly, in BCLC-C stage SIRT has proved a higher response rate than sorafenib, but it does not improve overall survival [82]. In earlier stages SIRT might help reduce the drop-out rate from transplant waiting lists [83] and in borderline resectable HCC SIRT might be associated not only with a better tumor control but also with a significant hypertrophy of the contralateral hepatic lobe [84].

HCC is one of the most chemo-resistant tumors, and systemic chemotherapy is currently not recommended for the treatment of HCC [85], although chemotherapy for HCC in non-cirrhotic patients is underexplored, requiring further research. The standard of care in first-line systemic therapy is sorafenib, a multikinase inhibitor, indicated for patients with good performance status (PS 1-2) and well-preserved liver function (Child-Pugh A) and advanced HCC (BCLC-C) or tumors progressing upon or unsuitable for locoregional therapies [33,85]. Patients without extrahepatic spread or those infected with HCV tend to benefit more from the therapy with sorafenib [86]. Sorafenib should be administered until radiologic progression of the lesions, when second-line therapy with regorafenib is recommended. Levantinib has demonstrated non-inferiority to sorafenib as first-line therapy in terms of overall survival for patients with advanced HCC (excluding a tumor burden >50% of liver volume or main portal vein invasion), PS 0-1 and Child-Pugh A, and was associated with higher response rates, longer time to progression and improved disease-free survival [87]. Second-line systemic therapies include regorafenib (approved for patients who tolerated sorafenib but experienced radiologic progression on sorafenib, with PS 0-1 and Child-Pugh A) [88], cabozantinib (as monotherapy for advanced or unresectable HCC, for patients previously treated with sorafenib) [89] and ramucirumab (for patients with advanced or unresectable HCC, baseline AFP ≥400 ng/ml and previously treated with sorafenib) [90]. Immune therapies with nivolumab, pembrolizumab and the dual therapy nivolumab+ipilimumab have recently received FDA approval as second-line therapy in advanced HCC, but EASL considers that the current data is insufficient for a clear recommendation.

Future directions in systemic therapies are based on identifying new pathways involved in the carcinogenesis of HCC that could become therapeutic targets. The higher prevalence of HCC in men has led to studies exploring the androgen receptor expression in HCC and a phase II study with enzalutamide [91]. Glypican 3 is a membrane protein involved in cell proliferation and a possible target for immunotherapy in HCC, with an ongoing research on manipulating the T-cell receptor to recognize glypican 3 [92-94]. Another interesting immunotherapy concept consists of the use of oncolytic viruses: T-VEC (a modified herpes virus) and Pexa-vec (a modified vaccinia virus), that at sufficient infectious doses are capable of inducing the autolysis of the tumor [95,96]. Sapanisertib, a strong mTOR inhibitor, has proved in vitro efficacy in HCC lines resistant to sorafenib [97], just like galunisertib [98], inhibitor of TGF-β signaling pathway, making these two drugs candidates for clinical trials.

Conclusions

In most of the cases HCC develops in the context of a well-defined underlying liver disease, thus being preventable. However, the incidence of HCC has been rising in the past years in the most European countries, pointing out the lack of awareness of the general population regarding liver diseases in general and HCC in particular. Due to the inappropriate surveillance for cancer and neglect of liver disease many patients with HCC are diagnosed at a more advanced stage, when curative treatment is no longer an option. These epidemiological observations underline the imperative need for public health policies addressed to preventing, detecting and treating chronic liver disease and for appropriate screening programs allowing the diagnosis of HCC at an earlier stage, suitable for curative treatment. Other major challenges in the management of HCC are represented by the need to optimally describe the sequencing of systemic therapy and the development of third-line therapies in advanced HCC. Ongoing research will probably provide new drugs targeting a wide variety of presumed pathogenic mechanisms involved in HCC carcinogenesis, but managing the irreversible cirrhosis and the hepatotoxic side effects will definitely remain crucial issues to address for each and every new therapeutic agent.

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