Therapeutic Perspective

CLINICAL INVESTIGATION

Personalized medicine in hepatocellular carcinoma: rationale and clinical data

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor. Its incidence is increasing in the West due to the expansion of hepatitis C virus infection and nonalcoholic fatty liver disease; globally the most important cause of HCC is chronic infection by hepatitis B virus. Due to the surveillance policy, HCC diagnosis at an early stage is increasing. Liver transplantation, hepatic resection, percutaneous ablation and transarterial chemoembolization have emerged as effective therapies with both curative and palliative intention. In 2008, a seminal paper was published in the *New England Journal of Medicine* in which Llovet and collaborators showed that sorafenib prolongs survival in the advanced stage of disease. This drug, an oral multikinase inhibitor, indicated the beginning of a new era in which the molecular classification of tumors and personalized treatments will be the main challenge.

Keywords: α-fetoprotein • cirrhosis • hepatocellular carcinoma • liver transplantation • screening • sorafenib • transarterial chemoembolization • treatment

Epidemiology, surveillance & diagnosis

Hepatocellular carcinoma (HCC) accounts for 70–85% of the total liver cancer burden worldwide [1]. HCC is the fifth most frequently diagnosed cancer in men, and the second cause of cancer-related death. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. More than 740,000 new HCC cases and more than 690,000 HCC deaths occur yearly worldwide [1]. These numbers reflect that HCC is generally diagnosed at a final state, when symptoms are present, and at this stage mean survival time is approximately 1 year. By contrast, if HCC is detected at an earlier phase of the disease, in asymptomatic patients, there are possibilities of receiving a curative treatment to achieve 70% of 5-year survival.

Hepatitis B virus (HBV) infection accounts for 60% of total liver cancer in developing countries and for approximately 23% in developed countries, while hepatitis C virus infection is responsible of 33% of HCC cases in developing areas and 20% in developed places. In the USA and several other low-risk western countries, alcohol-related cirrhosis and nonalcoholic fatty liver disease (NAFLD) associated with obesity are thought to account for the majority of HCC. An association between genetic polymorphisms of enzymes participating in the metabolic pathway of alcohol (especially aldehyde dehydrogenase 2 and null gluthatione *S*-transferase M1 genotype polymorphisms) and the augment of HCC has been proposed [2,3]. Incidence of HCC is increasing in many parts of the world, including the USA and Europe, secondary to the obesity epidemic and the rise in hepatitis C virus infection through continued transmission by injection drug users [1]. The prevalence of NAFLD is approximately 10–30% in adults and it is increasing due to the

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widespread rise in obesity and diabetes [4]. The natural history and prognosis of NAFLD is not well known, and the carcinogenic effect of NAFLD could be in part explained by the deleterious effect of insulin resistance, leptin and oxidative stress [5,6].

While liver cirrhosis is the leading cause of HCC in Western countries, HBV chronic infection is the most common cause in Africa and in the countries of South-East Asia. For this reason, those patients that would be treated if HCC was diagnosed should be included in a surveillance program. Surveillance programs should be applied in patients with a high risk of HCC with the objective of decreasing mortality from the disease. If the annual incidence of HCC is higher than 1.5% it is cost effective to include these patients in screening programs [7]; this population is listed in **Box 1**. According to the most recent American Association for the Study of Liver Diseases guidelines, personnel in the studies must undergo a hepatic ultrasound (US) every 6 months [8]. However, several teams continue to advocate for the value of α-fetoprotein (AFP) as a screening tool [9]. US has been reported to have a sensitivity of 65–80% and a specificity greater than 90% when used as a screening test [10] to detect small tumors in a cirrhotic liver. By contrast, serological tests are not useful in the surveillance setting because their sensitivity to detect initial tumors is generally lower than 60% [11–13]. AFP is the biomarker most commonly tested, with a sensitivity of 60% if the normal cutoff of 20 ng/ml is used. If the cutoff is raised to 200 ng/ml, the sensitivity drops to 22%. Other tests used to diagnose HCC are des-γ-carboxy prothrombin, also known as prothrombin-induced by vitamin K absence II, the ratio of glycosylated AFP (L3 fraction) to total AFP, α-fucosidase and glypican 3. None of these have been properly studied as screening tests and, at present, they cannot be recommended [14].

Once a suspicious nodule is detected during US surveillance, the patient must be driven to a referral center because it has a high likelihood of being HCC. These patients should stop the screening program, receive enhanced follow-up and adhere to recall policies to determine if the identified abnormality fulfils HCC criteria [8]. Guidelines firmly recommend the management of HCC patients by a multidisciplinary experienced team of hepatologists, radiologists, oncologists and surgeons. The complexity of HCC relies on the underlying chronic liver disease, which, not only is the cause of cancer, but could also be the main contraindication for the election of specific treatments and it could be the most important prognostic factor in some patients.

Noninvasive diagnosis criteria for HCC have recently been modified and prospectively validated [15–17]. In a cirrhotic liver, one nodule higher than 1 cm with a typical behavior after intravenous contrast injection in a multidetector computed tomography (CT) scan or in a dynamic MRI study can be firmly diagnosed as an HCC. This typical pattern consists of an arterial hyperenhancement followed by a rapid contrast washout with hypoenhancement in the portal or delayed phases. If the nodule presents with this pattern in the contrast-enhanced US, it could be misdiagnosed with a cholangiocarcinoma and this is the reason supporting the exclusion of this imaging technique as a diagnostic tool for HCC [18]. Progression from nonmalignant nodules to HCC implies the loss of visualization of portal tracts and development of new arterial vessels and nontriadal arteries (not accompanied by bile ducts), which become the dominant blood supply in overt HCC lesions [19]. For nodules less than 1 cm in size, the guidelines recommend a narrow follow-up with US every 3–4 months. If the lesion grows or changes in appearance, diagnostic work-up has to be performed [8]. If the nodule is not characteristic in the CT scan or MRI study, or it appears upon a noncirrhotic liver, biopsy is mandatory. In recent years, several immunohistochemical markers that could be used to differentiate HCC from other liver lesions, especially in small tumors where differential diagnosis with high-grade dysplastic nodules is a major challenge, have been described. Some of these biomarkers are clathrin heavy chain in combination with glypican 3 (GPC3), heat shock protein 70 and glutamine synthetase [20]. Of the nodules less than 2 cm detected by screening, approximately 60% will require a biopsy and more than 30% will require a second biopsy to exclude a false-positive result.

Box 1. Patients at risk of hepatocellular carcinoma who should be included in surveillance programs.

- Hepatitis B carriers
  - Asian males older than 40 years and females older than 50 years
  - All cirrhotic hepatitis B carriers
  - Family history of hepatocellular carcinoma – Africans over 20 years
- Nonhepatitis B cirrhosis
- Hepatitis C carriers
  - Alcoholic cirrhosis
  - Genetic hemocromatosis (mutation *C282Y* in HFE)
  - Primary biliary cirrhosis

HFE: Human hemochromatosis protein.
Adapted from [8].

Staging & treatment

Once HCC has been diagnosed the next step should be the staging. By contrast with other solid tumors, the TNM classification has been shown to be less useful in other solid cancers. The Barcelona Clinic Liver Cancer (BCLC) staging system **(Figure 1)** has been endorsed by the American Association for the Study of Liver Diseases and many European scientific societies as

the best prognostic model for HCC because it links the stage of the disease with the possible treatments [21]. The BCLC was first created in 1999, by observing the survival and prognostic factors of different groups of patients enrolled in several randomized trials [22]. Many other groups in Europe and in the USA have extensively validated the BCLC *a posteriori* [23–25]. Each stage is defined by a multidimensional design composed of the Eastern Cooperative Oncology Group performance status [26] (ECOG-PS; Table 1), liver function expressed by Child-Pugh score (Table 2) and tumor burden. The combination of these three aspects results in five different stages.

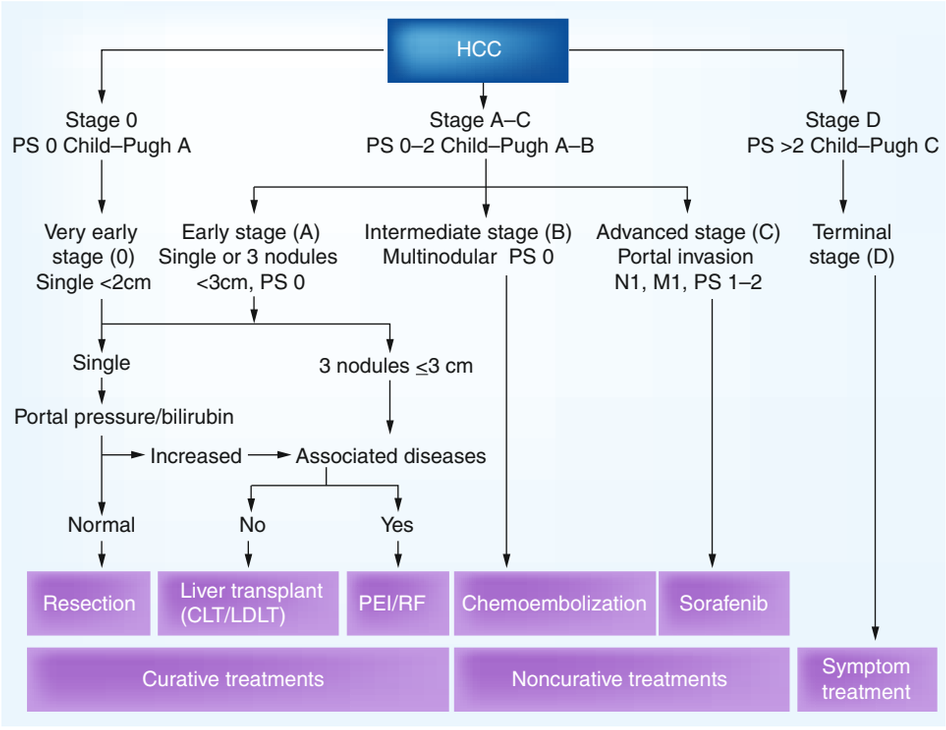

Figure 1. Barcelona Clinic Liver Cancer staging and treatment strategy.
HCC: Hepatocellular carcinoma; PS: Performance status.
Reproduced with permission from [21].

STAGE 0, very early HCC: ECOG-PS 0 (asymptomatic, normal quality of life), single tumor less than 2 cm, Child–Pugh A (normal liver function). In these cases a treatment with curative intention is indicated. Classically, surgical resection was the first option for these patients, but recently, several cohort studies [27,28], nonrandomized control trials [29–31], a Markov model [32] and a meta-analysis [33] have shown a similar efficacy of radiofrequency ablation in terms of local control of disease, rate of recurrence and long-term survival. Approximately 15% of HCC patients are diagnosed at this stage in western countries.

Surgical resection is the therapy of choice in patients with normal livers. By contrast, in those cases with underlying cirrhosis, candidates should be carefully selected because they are at risk of liver decompensation due to the procedure. Absence of esophageal varices, normal size of spleen, platelet counts higher than 100,000/mm^3, normal bilirubin and a hepatic venous pressure gradient less than 10 mmHg, or indocyanine green retention rate at 15 min (ICG15) <20% in Japan, define a small selective group of patients (less than 5%) that could be ideal candidates for segmental resections. Very early HCC have an excellent prognosis with 5-year survival rates greater than 80%.

STAGE A, early HCC

ECOG-PS 0, one HCC or three nodules less than 3 cm, Child–Pugh A–B. Approximately 30% of patients with HCC are diagnosed in stage A in western countries. By contrast, this figure rises up to 70% for those patients included in surveillance programs. They are candidates for therapies with curative intention, such as liver resection, liver transplantation or percutaneous ablation. Liver resection could be the first option in those cirrhotic patients with single nodules, normal bilirubin, Child–Pugh A and a hepatic venous pressure gradient less than 10 mmHg; as well as those patients with healthy livers. If patients cannot be resected they should be submitted for liver transplantation. In those cases with formal contraindications for resection and liver transplantation (i.e., severe extrahepatic

Table 1. Eastern Cooperative Oncology Group-performance status.

Grade	ECOG
0	Fully active
1	Restricted in strenuous activity but ambulatory and able to carry out sedentary of light work
2	Capable of self-care but unable to work; ambulatory more than 50% of waking hours
3	Limited self-care, in bed or chair more than 50% of waking hours
4	Completely disabled; totally confined to bed or chair
5	Dead

ECOG: Eastern Cooperative Oncology Group.
Adapted from [26].

Table 2. Child–Pugh score.

Variable	1 point	2 point	3 point
Total bilirubin	<2 mg/dl (<34 µmol/l)	2–3 mg/dl (34–50 µmol/l)	>3 mg/dl >50–µmol/l
Total albumin	>3.5 g/dl (>35 g/l)	2.8–3.5 g/dl (28–25 g/l)	<2.8 g/dl (<28 g/l)
International normalized ratio	<1.7	1.7–2.2	>2.2
Prothrombin time	>50%	30–50%	<30%
Encephalopathy	Absent	Grade I–II	Grade III–IV
Ascites	Absent	Mild, medically controlled	Not medically controlled

Adapted from [67,68].

comorbidities), percutaneous ablation should be indicated. Although there were some controversies in the past about which was the best technique, radiofrequency ablation is generally the preferred percutaneous procedure. Some randomized controlled trials [34,35] and meta-analysis have demonstrated that radiofrequency is better in terms of local control of the disease for lesions between 2 and 3 cm; in addition, this better control of disease impacts directly on survival [36,37].

This is the time where decisions have to be taken, but individualized treatments should be designed. For instance, a deep HCC situation may imply the need for large hepatectomy and, thus, become too harmful for a cirrhotic liver; location of HCC may impede the performance of percutaneous radiofrequency if the nodule is just under the capsule of the liver or if it is located near a hollow viscous or besides a large vessel. In the first situation, the subcapsular location can increase the risk of seeding if the HCC requires a direct puncture without a protective border of a nontumoral liver [38]; in the second one there could be a risk of perforation (bile bladder, colon and so on) during the procedure if it is not performed by experienced staff. Finally, in the third situation, the proximity of a large vessel can prevent the achievement of a high temperature in the part of the nodule nearest to the vessel, with a risk of incomplete necrosis in this area.

The second part of this individualized therapy tailored to the characteristics of the patient is the quality and prognosis of each treatment that can be applied at each center. The medical team must know what the expected result of each treatment is, and must try to obtain a complete response of the disease with the best and least risky therapies. Complete response together with the absence of symptoms and good liver function are the main prognostic factors that influence the long-term survival of those HCC patients in which local and regional therapies are used [39,40].

Ideally, the best therapy for HCC is liver transplantation (LT). HCC is the only solid cancer that can be cured with transplantation. Theoretically this will be the best therapy because it removes the cancer and the underlying predisposing disease. However, the shortage of donors and the progressive increase in the number of candidates imply a longer time on the waiting list, with risk of dropout due to the growth of tumor or to liver decompensation. Several solutions have been offered: an allocation policy based on the model for end-stage liver disease system, increasing the number of donors (by means of living donor liver transplantation, nonbeating donors and split transplantation) and application of treatment whilst on the waiting list to try and avoid the enlargement of the nodule. It has been established that living donor liver transplantation will be cost effective if the waiting list is longer than 7 months. This technique has several ethical considerations due to the morbidity (14–21%) and mortality (0.25–1%) described in donors [41]. Bridge treatments such as surgery, percutaneous ablation and chemoembolization have been shown to be useful if the waiting list is longer than 6 months. However, all studies have failed to demonstrate a longer graft and patient survival after LT compared with those patients without treatment whilst on the waiting list [42,43].

On the other hand, some groups have promoted an expansion of HCC criteria for enlisting [44]. The most common criteria accepted for LT are one nodule less than 5 cm or up to three nodules less than 3 cm, the so-called Milano criteria [45]. With application of these criteria there will be less than 15% recurrence of HCC after LT and survival may be higher than 70% at 5 years. Unfortunately, recently the dropout rate has increased up to 30% at 12 months in many centers, with a clear impact in the results of LT from an intention-to-treat perspective; herein, survival has declined to less than 60% at 5 years, in clear competition with ablation techniques in some cases. In this situation, it is difficult to accept a general expansion of criteria for LT; however, recent publications such as the Metroticket of Mazzaferro [46] could provide a guide to know what would be the result of a modest expansion in size or number of nodules. The main drawback of expansion is the impossibility to detect the presence of microvascular invasion at the time of the indication of LT. High levels of AFP together with the presence of microvascular invasion, satellites and poor degree of differentiation, are independent factors of recurrence after LT. These prognostic factors should be kept in mind when considering the use of scarce organs in patients with suboptimal outcome.

Therefore, the medical team should not only know how the patient is (comorbidity and attitude towards the treatment), but also should consider the liver reserve capacity and the expected result of each treatment modality.

The main problem derived from resection and percutaneous ablation is the high rate of recurrence (70% at 5 years). Stopping drinking, losing weight, improved management of diabetes and antiviral therapies are very useful to prevent liver impairment, but at present, they do not act on the already disseminated tumor clones that will result in early recurrences. In patients who are candidates for resection, the presence of satellites or microvascular invasion recurrence will impair prognosis, and if the patients had been transplanted the risk and survival would have been significantly better [47]. Because of this, the recommendation is to propose LT because of high risk of recurrence. The decision should not be delayed because, when recurrence appears, multifocality will be the rule and LT will be contraindicated.

Unfortunately, there is no drug or therapy generally accepted in the adjuvant setting, and this is an important issue that has not been resolved yet. The recruitment to the STORM trial (NCT00692770) has recently finished, with more than 1100 patients enrolled. (Please see [101] for further details on all trials.) Primary outcome is recurrence-free survival and final collection of data for this end point is expected in November 2013. Other systemic therapies have been tested at this moment, that is, interferon [48], acyclic retinoid [49] and adoptive immunotherapy [50], with negative results and no use in HCC chemoprevention at this moment. NCT00460681 is a Phase III, randomized, controlled trial, with active recruitment at this moment, in which patients with HBV-related HCC receive thymopentin (TP5) for 3 months after curative resection.

STAGE B, intermediate HCC

This is the most heterogeneous group of patients. Multinodular tumors without vascular invasion or extrahepatic disease, ECOG-PS 0 and Child–Pugh class A or B characterize them. In the absence of contraindications (Box 2) [51] transarterial chemoembolization (TACE) is the first therapeutic option. This treatment achieves a survival rate as high as 50% at 4 years in well-selected patients, although the mean survival described in classical trials is 14–16 months [52,53]. Recently, new devices have been described, such as DC-Beads, which are more tolerable and effective in frail cirrhotic patients [54,55]. However, in some cases with low tumor burden or in those cases with renal failure or hepatofugal portal flow, TACE can be replaced with extended indication of percutaneous ablation or with systemic therapy. Several trials are underway in which TACE is combined with a percutaneous ablation procedure and with sorafenib. NCT00855218 (SPACE study) is a Phase II trial in which patients of BCLC-B stage are randomized to TACE plus sorafenib versus TACE plus placebo. Final data collection date for primary outcome measure (time to progression) was May 2011. In addition, a randomized, double-blind, multicenter, Phase III study of brivanib versus placebo as adjuvant therapy to TACE is currently running (NCT00908752).

Box 2. Contraindications for transarterial chemoembolization.

- Absolute contraindications
  - Decompensated cirrhosis (Child–Pugh B > 8 points) including hepatorenal syndrome, jaundice, encephalopathy and refractory ascites
  - Extensive tumor of both lobes
  - Extensive reduced portal vein flow (nontumoral or hepatofugal)
  - Technical contraindications to intra-arterial hepatic treatment
  - Creatinine >2 mg/dl or clearance of creatinine <30 ml/min
- Relative contraindications
  - Tumor size >10 cm
  - Underlying atherosclerosis
  - Chronic lung disease that requires oxygen support or multidrug treatment
  - Untreated varices at high risk of bleeding
  - Bile-duct occlusion or incompetent papilla due to stent or surgery

Adapted from [51].

In recent years, internal endoarterial embolization with yttrium^{90} has emerged as a novel treatment of HCC [56]. In limited series this technique was able to produce similar results to TACE, and in some Child–Pugh class A patients with large tumors in which TACE does not provide effective treatment, internal radioembolization might be more advantageous. It is thought that it will probably never be possible to perform a face-to-face trial with TACE versus yttrium^{90} in BCLC-B patients because of the complexity of technology needed to perform radioembolization, which is only available in selected centers, and because the estimated number of patients needed will be more than 1000 [57]. So, in these circumstances the highest level of evidence will be provided by cohort and case–control studies. Recently, Sangro *et al.* published the largest cohort of HCC patients (325 at eight European centers) treated with yttrium^{90}-labeled resin microspheres. Over a quarter had intermediate staging (BCLC B, 26.8%), with a mean overall survival of 16.9 months (95% CI: 12.8–22.8 months) [58].

Transplantation within downstaging protocols is also an extremely valuable therapeutic option despite the fact that there are two main problems to face: first, lack of donors with longer waiting list period and increasing risk of dropout; second, just a minority of intermediate HCC patients could be, in theory, candidates for downstaging treatments.

In the NCT00105443 SHARP trial approximately 30% of patients were enrolled at an intermediate stage, with a maintenance of survival of 20 months and time to progression of 6.9 months for those treated with sorafenib in comparison with placebo (11.4 and 4.4 months

for the two variables, respectively) [59]. In such a scenario, it is conceivable to offer sorafenib to those intermediate HCC patients refractory to TACE with multinodular progression after at least two sessions.

STAGE C, advanced HCC

These patients are characterized by a mild impairment in their general status (ECOG-PS 1–2) or by extrahepatic disease and/or vascular invasion. Until 2008, HCC was an orphan cancer without a first line of therapy for advanced stage. With the publication of the SHARP trial [59], followed by the results of the Asian–Pacific trial [60], sorafenib was approved in the USA, Europe and Asian countries, and now it is the standard reference of Child–Pugh class A patients with advanced HCC. Sorafenib is a small, orally active, multikinase inhibitor that targets the Ras/Raf/MEK/ERK pathway in the tumor cell and exerts an antiangiogenic effect by targeting VEGFR1, 2 and 3 and PDGFR-β, both of which are tyrosine kinases. In the SHARP trial, 602 patients who had not received prior systemic therapy and who were Child–Pugh A, were double-blind randomized to receive sorafenib 400 mg twice daily versus placebo. The primary end point was overall survival, which was significantly longer in the sorafenib group than in the placebo group (10.7 vs 7.9 months; $p < 0.001$; hazard ration: 0.68). Time to progression was also longer (5.5 vs 2.8 months; $p < 0.001$) and disease control rate was significantly better in the sorafenib group than in the placebo group (43 vs 32%; $p = 0.0002$).

Results of sorafenib in HCC conducted to a rapid generation of trials to test different targeted therapies and currently there are more than 50 agents under evaluation (Table 3). Some of them have proven too toxic and risky for cirrhotic patients (e.g., sunitinib [61,62] an anti-PDGFR. Two Phase II trials with sunitinib described a median survival of 10.5 months, but 5–10% of liver-related deaths, and a Phase III trial evaluating sunitinib versus sorafenib has been stopped prematurely because of an excess of toxicity together with lack of efficacy). Some others have shown just a modest effect, for example, nolatrexed [63], or more recently selumetinib [64]. Bevacizumab, a monoclonal antibody against VEGF-A that also blocks angiogenic signals from tumor microenvironment, is the third most frequently evaluated drug, with 19 trials in HCC, after sorafenib with 128 and everolimus (inhibits the serine/threonine kinase mTOR) with 22. Currently, there are six kinase inhibitors being tested in Phase III pivotal trials for regulatory approval, to change the standard of care. These trials include first-line (sorafenib, erlotinib, brivanib and linifanib), second-line (everolimus and brivanib) and adjuvant therapy, after resection or ablation (sorafenib), or prevention of recurrence after liver transplantation (rapamycin) [65].

Brivanib is an orally available dual inhibitor of VEGFR and FGFR. A Phase II, open-label study conducted to evaluate the effects of brivanib alaninate 800 mg as either first- or second-line therapy in patients with unresectable locally advanced or metastatic HCC has recently been reported [66]. A total of 55 patients were treated and evaluated for response. Median overall survival (95% CI) was 10.0 (6.8–15.2) months. Based on these positive results, a Phase III randomized study of brivanib versus sorafenib was initiated (NCT00858871) to explore the potential additional clinical efficacy brivanib provided through inhibition of FGFR.

Finally, internal radioembolization has also proved to be useful in advanced patients. Over 50% of the multicentric European cohort treated with yttrium^{90}-labeled

Table 3. Trials with active recruitment of molecular-targeted therapies in hepatocellular carcinoma.

Drugs	Trial phases	Number of trials	Molecular targets
Sorafenib	1, 1–2, 2, 3, 4	128	BRAF, VEGFR, PDGFR
Bevacizumab	1, 1–2, 2	19	VEGF
Erlotinib	1, 1–2, 2, 3	15	EGFR
Everolimus	1, 1–2, 2, 3	22	MTORC1
Brivanib	1, 2, 3	6	FGFR, VEGFR, PDGFR
Sunitinib	2, 3	10	VEGFR, PDGFR, KIT
Rapamycin	1, 2–3, 3	22	MTORC1
AZD6244	1–2, 2	3	MEK
Bortezomib	1, 2	3	Proteasome
TAC-101	1–2, 2	4	RAR-α
Cediranib	1, 2	2	VEGFR
Cetuximab	1, 2	2	EGFR
Cixutumumab	1, 2	3	IGF-1R
Temsirolimus	1, 2	22	MTORC1
Linifanib	2, 3	2	VEGF, PDGFR
PI-88	2, 3	2	Endo-D-glucuronidase heparinase
ARQ197	1, 2	4	MET
BIBF1120	2	2	VEGFR, PDGFR, FGFR
Dasatinib	2	2	BCR-ABL
GC33	1	2	GPC3
Gefitinib	2	2	EGFR
Lapatinib	2	2	EGFR, HER2/neu
Licartin	2, 4	2	HAb18G/CD147
Pazopanib	2	4	VEGFR, PDGFR, KIT
Alvocidib	1, 2	1	Cyclin-dependent kinase

Adapted from [101].

resin microspheres had advanced BCLC C stage, (56.3%) and they reached a mean overall survival of 10.0 months (95% CI: 7.7–10.9 months) [58].

The most important limitation for the expansion of application of molecular targeted therapies in HCC is the presence of underlying liver cirrhosis and portal hypertension. They provide a special situation in which efficacy for HCC is not counteracted by toxicity.

STAGE D, end HCC

Those patients with heavily impaired liver function who are not candidates for liver transplantation and/or major physical impairment (ECOG-PS more than 2), with no more than 3 months of mean expected survival, should receive only symptomatic treatment to avoid needless distress. At this point it is also very important to have a multidisciplinary approach under the direction of the palliative healthcare teams.

Future perspective

Molecular targeted therapies for the treatment of HCC are a very promising approach, clearly established by the breakthrough results of sorafenib. Basic and translational research focused on understanding the pathways, receptors and kinases implicated in pathogenesis, invasion and metastases of HCC have helped to identify many novel potential targets that need to be further evaluated in preclinical and clinical trials. The key would be to combine different drugs with effects over distinct functions in tumor cells (i.e., antiangiogenic drug plus epigenetic plus proapoptotic) adjusted to the different types of HCC, as the initial molecular HCC classifications are timidly showing us. There are also increasing data about the extreme importance of the extracellular matrix and microenvironment for the initiation and maintenance of HCC. All this basic information should be incorporated into the clinical setting and in the near future we could see personalized medicine in HCC.

In a few years we will dispose of a therapeutic arsenal to treat HCC with single or combined agents. The better knowledge of the molecular abnormalities leading to cancer and the specific profile associated with a better or worse prognosis will allow a biology-based prediction of the outcome of patients, together with a specific treatment selection and prediction of its long-term success.

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Executive summary

- In western countries, nonalcoholic fatty liver disease, chronic infection by hepatitis C virus and alcohol are the main causes of hepatocellular carcinoma (HCC). These patients should be screened for cirrhosis and submitted to surveillance programs if it is present.
- Surveillance of HCC should be made with an abdominal ultrasound (US) every 6 months. Expert, properly trained staff should perform this US.
- Diagnosis of HCC can be made by noninvasive criteria in the setting of liver cirrhosis, by multidetector computed tomography scan and MRI studies in which HCC nodules are typically hyperenhanced in the arterial phase followed by rapid washout in the portal and delayed phases. Contrast-enhanced US should not be used. Recall policies should be encouraged if atypical nodules are detected.
- Multidisciplinary teams at referral centers should manage these patients. The Barcelona clinic liver cancer staging system should be initially used to define the best treatment tailored to the patient characteristics.
- Liver transplantation, percutaneous ablation and surgical resection are considered curative therapies. Transarterial chemoembolization and sorafenib are the first line of treatment for those patients with HCC at intermediate and advanced stages, respectively.
- At the advanced stage, those patients with radiological progression or intolerance to sorafenib should be enrolled in a randomized control trial to study the effect of other molecular-targeted therapies.

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